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SYNTHESIS AND PROPERTIES
OF
THIENO- AND FURO- TROPONES

by

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ABSTRACT

The synthesis of thieno[3,2-b]tropones and furo[3,2-b]tropones by dehydrobromination of $\alpha\alpha$ -dibromoketones using lithium carbonate in anhydrous N,N-dimethylformamide is investigated. Synthetic routes to furo[3,2-b]tropone and to three substituted thieno[3,2-b]tropones are presented, and attempts to prepare thieno[3,2-b]tropone are reported.

The isolation of a photodimer from the photolysis of 2-methylthieno[3,2-b]tropone in methanol is reported, and a possible structure for this compound is proposed.

PART 1

REVIEW

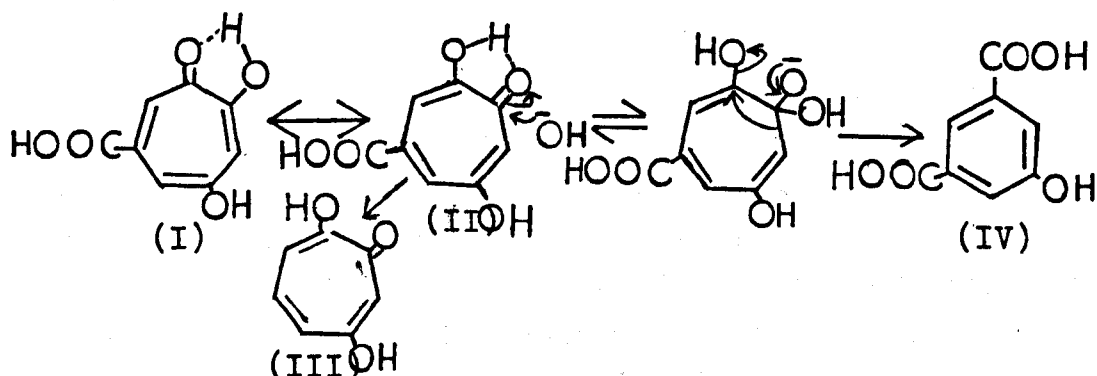
Monocyclic troponoid compounds.

The first example of a monocyclic troponoid compound appeared in the literature in 1945, when Dewar (1) proposed a structure for stipitatic acid, a mould metabolite of *Penicillium Stipitatum*. This compound had been isolated in 1942 by Birkinshaw, Chambers and Raistrick (2) and had a molecular formula $C_8H_6O_5$; it was a dibasic acid having three active hydrogens and gave a deep red colour with ferric chloride. It did not react with bromine, although on treatment with bromine in 80% acetic acid it formed a monobromostipitatic acid which had properties similar to those of stipitatic acid itself. Decarboxylation using copper in quinoline gave a monobasic acid having a molecular formula $C_7H_6O_3$, which also gave a deep red colour with ferric chloride. Alkali fusion of stipitatic acid gave 5-hydroxy-isophthalic acid in good yield. The compound was soluble in concentrated acid, but was precipitated on dilution; it had no ketonic properties.

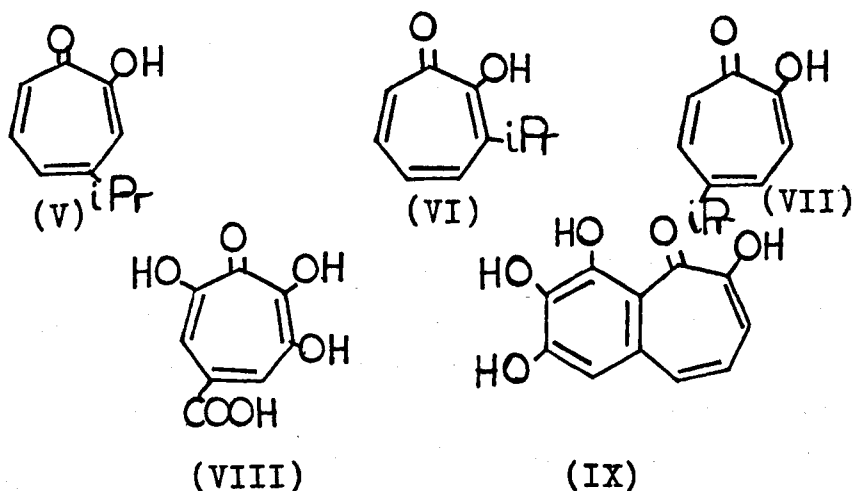
Dewar reasoned that the lack of reaction with bromine indicated some kind of aromatic compound, but that the ready conversion to 5-hydroxy-isophthalic acid precluded any structure containing a benzene nucleus or having an oxygen atom in the ring. Dewar therefore proposed the structure (I) in which the carbonyl group and the hydroxyl group adjacent to it combine to form the second acidic function, which prevents the compound from exhibiting the normal properties of a ketone. The compound will exist in the two tautomeric forms (I) and (II), and on treatment

with copper in quinoline will undergo decarboxylation to give 6-hydroxy- α -tropolone (III). The rearrangement under basic conditions to yield 5-hydroxy-isophthalic acid (IV) will proceed by the mechanism shown in Scheme 1.

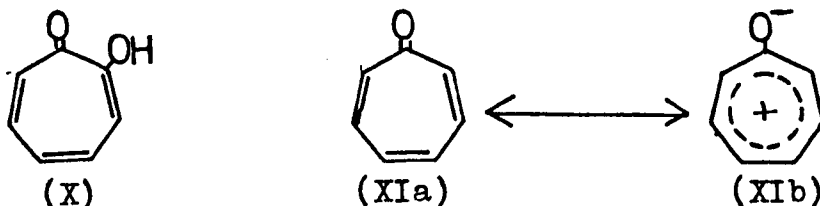
SCHEME 1.



At about the same time that Dewar published his structure for stipitatic acid, work was being carried out on hinokitiol, an antibiotic isolated from the heartwood of Cupressaceae, and the structure assigned to this compound was 4-isopropyltropolone (V), (3). Many other compounds containing the tropone nucleus have been isolated from natural sources, including 3-isopropyltropolone (VI), (4), and 5-isopropyltropolone (VII), (5), (from various trees of the Cupressaceae family), the mould product puberulic acid (VIII), (6,7), and the red colouring matter purpurogallin (IX) (8,9).

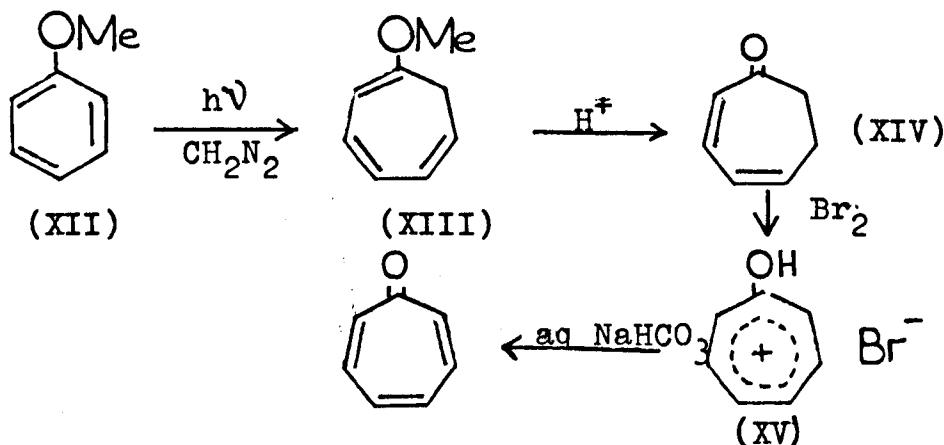


Dewar (1) postulated that the stability of stipitatic acid was due to the tautomerism involving the carbonyl and adjacent hydroxyl groups, and that therefore the parent compound was tropolone (X). It was subsequently realized that the stability arose from the potential ability to form a 6π electron system which, according to Hückel's Rules, would be particularly stable, and that therefore the parent compound must be tropone, which would have the two mesomeric forms (XIa and XIb). This also explained the solubility of stipitatic acid in strong acids, as protonation of the tropone (and of compounds containing the tropone nucleus) should result in salt formation in which the tropone cation is involved. The dipole moment of 4.3D (10,11,12) for tropone was at that time thought to be sufficiently high in comparison with that for cycloheptanone (3.04D) (13) to justify the claim that the stability of tropone was due to the fact that it existed mainly in the dipolar form (XIb). However, in 1967, Bertelli and Andrews (14) published a paper in which they compared the dipole moment of tropone with those of many similar model compounds; they concluded that the experimental value was sufficiently close to their predicted value for the discrepancy to be accounted for if as little as 4% of the tropone existed in the dipolar form (XIb), the remainder being in the neutral form (XIa).



In 1951 three groups of workers independently published the first syntheses of tropone. One method was based on the ring expansion of a benzene derivative, and the other two involved cycloheptanone derivatives. Doering and Detert (15) treated anisole (XII) with

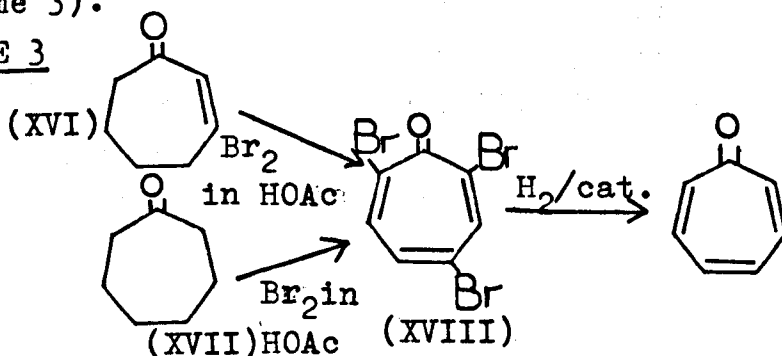
SCHEME 2



diazomethane in the presence of ultra-violet light to give a methoxycycloheptatriene (XIII), which, on treatment with acid yields a mixture of isomeric cycloheptadienones (XIV). Treatment of this mixture with bromine leads to hydroxycycloheptatrienylium bromide (XV), from which tropone can be isolated by shaking with aqueous sodium bicarbonate and extracting. (Scheme 2).

The other two syntheses published in 1951 both employed 2,4,7-tribromotropone (XVIII) as a precursor. Dauben and Ringold (16) prepared this in 38% yield from cyclohept-2-enone (XVI) by treatment with bromine in glacial acetic acid; conversion to tropone was effected by hydrogenation in ethanolic potassium acetate over palladium/barium sulphate catalyst and interrupting the reaction after 2.9 moles of hydrogen had been absorbed, giving a 40% yield of tropone. Nozoe and coworkers (17) prepared 2,4,7-tribromotropone in 50% yield by treating cycloheptanone (XVII) with bromine in glacial acetic acid; hydrogenation over Raney nickel catalyst gave tropone in 28% yield. (Scheme 3).

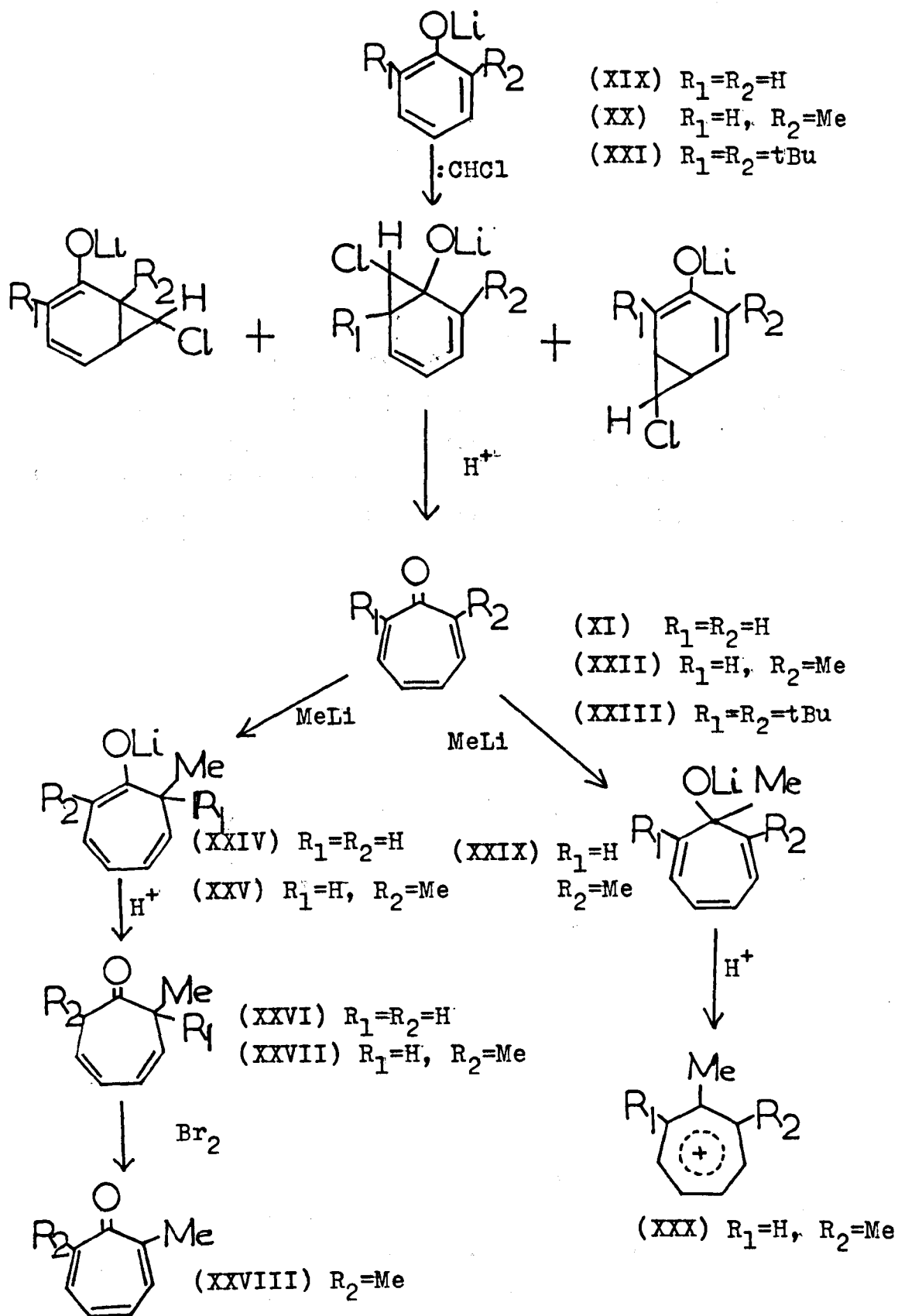
SCHEME 3



In 1952, Nozoe et al (18) published an alternative route to tropone from 2,4,7-tribromotropone by hydrogenation over a palladium charcoal catalyst which had been poisoned with either mercury or lead to prevent complete reduction of the molecule. This gave tropone in 40-50% yield.

The approach to tropone by means of ring expansion of benzenoid compounds has been further investigated. In 1961, Closs and Closs (19) reported the results of attempts to synthesise tropone by ring expansion of various lithium phenolate compounds by carbene insertion reactions. Chlorocarbene would be expected to insert into lithium phenolates as shown in Scheme 4, yielding initially a tropone. Chlorocarbene is prepared in situ from the reaction between methyllithium and methylene chloride (which is also used as a solvent); tropones are susceptible to attack by methyllithium either at the two position, in which case the product is a 2-methylcyclohepta-3,5-dienone, or at the carbonyl group, yielding a methyltropylum ion on acidification. Closs and Closs found that the relative proportions of the three possible products depended very much on the nature of the substituents R_1 and R_2 . Starting from lithium phenolate (XIX), 2-methylcyclohepta-3,5-dienone (XXVI) was isolated in 30% yield as the only product, which, on treatment with bromine, yielded 2-methyltropone (XXVIII). If lithium 2-methylphenolate (XX) was used, 2,7-dimethylcyclohepta-3,5-dienone (XXVII) was isolated in 15% yield, along with 2% of 1,2-dimethyltropylum ion (XXIX). If however one started from lithium 2,6-ditertiarybutylphenolate (XXI), 2,7-ditertiarybutyltropone (XXIII) was isolated as the sole product in 70% yield (based on recovered starting material). Presumably the bulky tertiarybutyl groups adjacent to the carbonyl group make it virtually impossible for the methyllithium

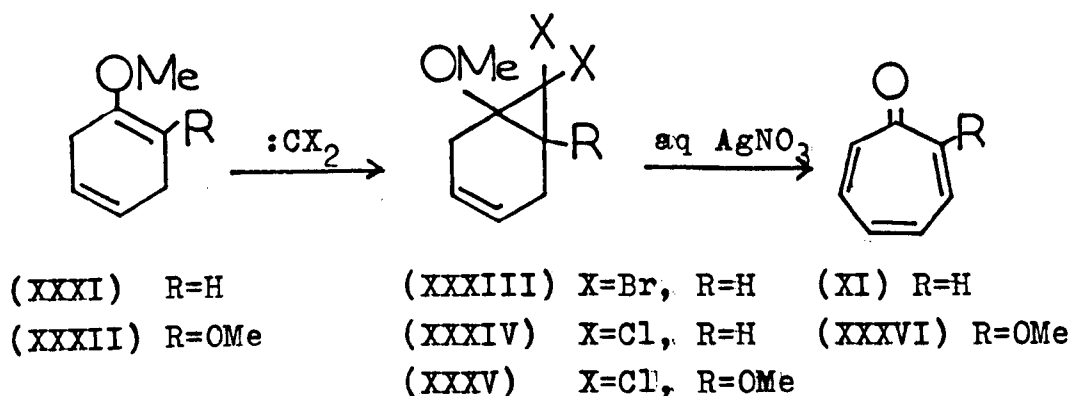
SCHEME 4



molecule to approach sufficiently closely for further reaction to occur once the tropone is formed. (Scheme 4).

In 1962, Birch, Graves and Stansfield (20) published a route which gave a 75% yield of tropone from 2,5-dihydroanisole (XXXI) (Scheme 5). Treatment of 2,5-dihydroanisole with dibromocarbene or dichlorocarbene gave the insertion products (XXXIII) and (XXXIV) in almost 100% yield. Treatment of the dibromoadduct with aqueous silver nitrate gave tropone in 75% yield; however, treatment of the dichloroadduct resulted in the recovery of starting material only. 2-Methoxyanisole (XXXII) reacted almost quantitatively with dichlorocarbene to give the insertion product (XXXV), which, on treatment with aqueous silver nitrate, gave α -tropolone methyl ether (XXXVI) in 65% yield.

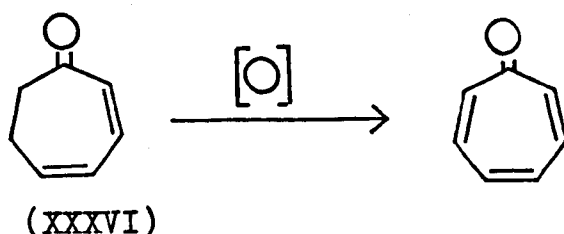
SCHEME 5



In 1956, Van Tamelen and Hildahl (21) published the results of an investigation into the possibility of synthesising tropone by the oxidation of cycloheptadienone. The methods investigated were: treatment with selenium dioxide, treatment with DDQ (2,3-dicyano-5,6-dichloroquinone), "air" oxidation

(stirring in aqueous sodium hydroxide for four days at room temperature), and the addition of one equivalent of bromine followed by refluxing overnight to give hydroxytropylium bromide, from which tropone can be obtained by shaking with aqueous sodium bicarbonate and extracting. The yields are given below; these yields were determined spectroscopically by measuring the absorption due to tropone in the ultra-violet region of the spectrum. No work has been done to determine whether the reactions can be scaled up and tropone isolated in comparable yields. (Scheme 6).

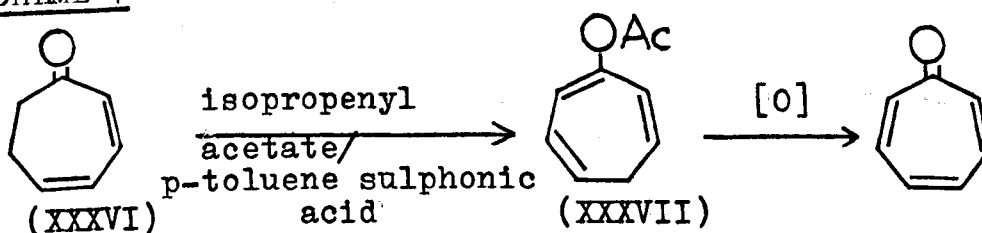
SCHEME 6



<u>Oxidising agent</u>	<u>Spectroscopic yield</u>
Selenium dioxide	70%
DDQ	10%
"Air"	38%
Bromine	75%

The same paper also gave details of attempts to prepare tropone from the enol-acetate of cycloheptadienone(XXXVII), which is prepared from cycloheptadienone by treatment with isopropenylacetate in the presence of p-toluene sulphonic acid. (Scheme 7)

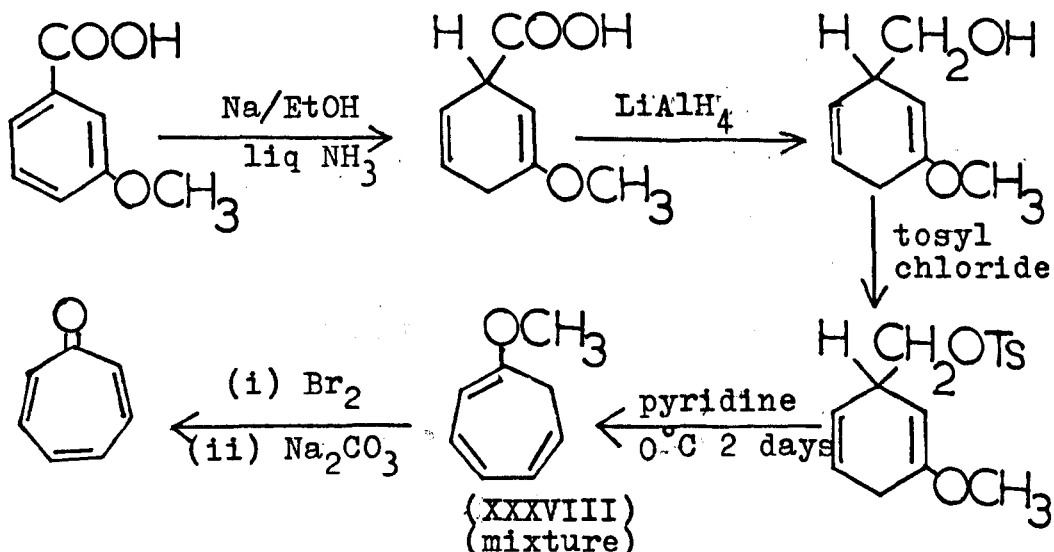
SCHEME 7



Selenium dioxide in pyridine, lead tetraacetate and N-bromosuccinimide in allyl bromide all gave spectroscopic yields of less than 29%; treatment with perbenzoic acid followed by mineral acid hydrolysis of the intermediate formed gave tropone in 55% spectroscopic yield. As with the other work, these experiments were carried out on very small quantities, and no work has been done to determine whether these yields can be achieved in preparative work.

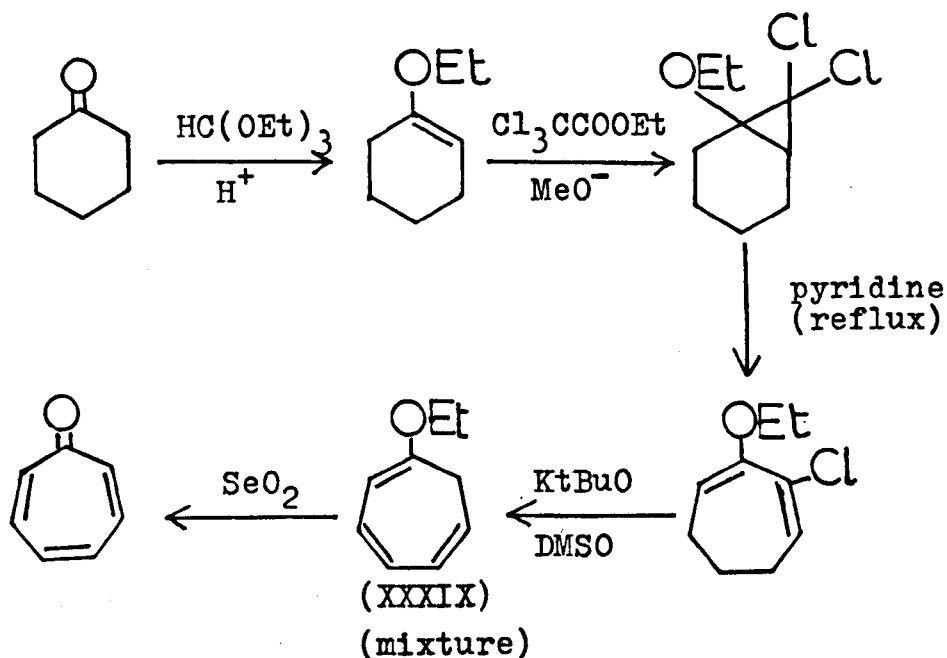
Reports have been published of routes to tropone by oxidation of alkyl tropyl ethers; in 1961 Chapman and Fitton (22) reported that methyl tropyl ether (XXXVIII) on treatment with bromine and subsequent treatment with base gave tropone in low yield. The methyl tropyl ether was prepared from 2-methoxybenzoic acid by Birch reduction followed by treatment with lithium aluminium hydride to give 2-hydroxymethyl-6-methoxycyclohexa-1,4-diene in 50% yield; treatment of this with p-toluene sulphonylchloride followed by solvolysis in pyridine (standing for 2 days at 0°C) gave a mixture of methyltropyl ethers in 38% yield.(23). (Scheme 8).

SCHEME 8



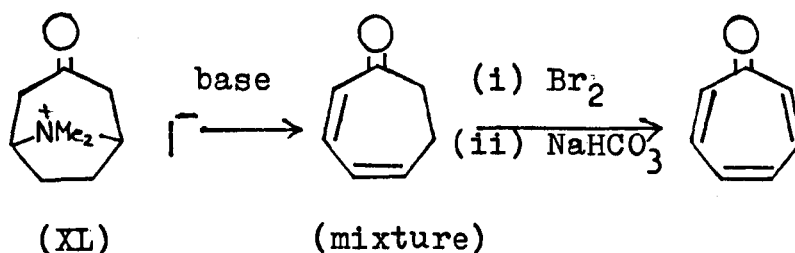
In 1965, Parham and coworkers (24) reported a similar preparation in which oxidation of ethyl tropanyl ether (XXXIX) with selenious acid in boiling absolute ethanol gave a 38% yield of tropone, based on the absorption spectrum of the reaction mixture measured at 228, 231.5, 224 and 312.5 nm. Ethyl tropanyl ether was prepared by insertion of dichlorocarbene into 1-ethoxycyclohexene followed by boiling in pyridine to give 2-ethoxy-3-chlorocyclohepta-1,3-diene, which was dehydrochlorinated by treatment with potassium tertiary butoxide in dimethyl sulfoxide (25). 1-Ethoxycyclohexene was prepared from cyclohexanone by conversion to the diethyl ketal in 88% yield (26), which on treatment with acid gave the required product in 93% yield (27). (Scheme 9).

SCHEME 9



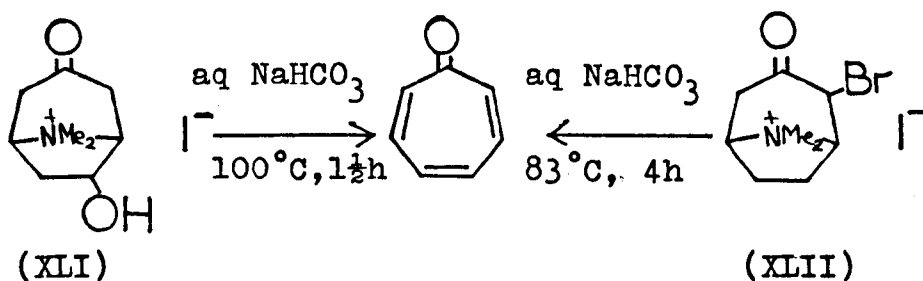
In 1887, Einhorn (28) treated tropinone methiodide (XL) with base and heated the product with bromine. Although he was unaware of it, he had prepared a hydroxytropylum salt for the first time. In 1953, Meinwald and coworkers (29) repeated this work (Scheme 10) and showed that treatment of tropinone methiodide with base (e.g. aqueous sodium carbonate, sodium bicarbonate or silver oxide) followed by steam distillation leads to a mixture of cycloheptadienones in up to 35% yield by elimination of dimethylamine. The addition of bromine, followed by heating, gives hydroxytropylum bromide, from which tropone can be isolated in the usual way.

SCHEME 10



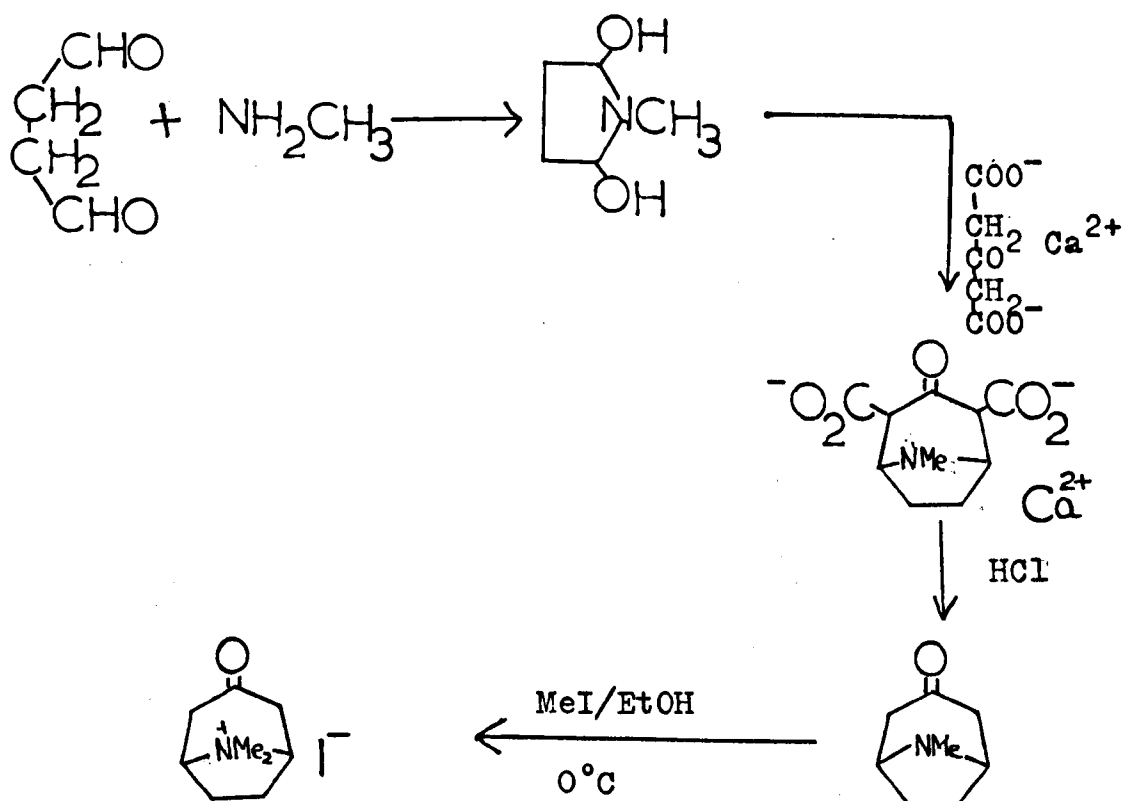
Van Tamelen et al (30) investigated the possibility of a one-step synthesis of tropone from a tropinone methiodide derivative which could also eliminate one molecule of a simple compound, such as water or hydrogen bromide, to provide the further degree of unsaturation required. In 1965 they reported that heating 4-hydroxytropinone methiodide (XLI) on a steam bath for 1.5 hrs. with aqueous sodium bicarbonate gave tropone in 82% yield, and that similar treatment of 2-bromotropinone methiodide (XLII) gave tropone in 60% yield. These reactions were carried out on a small scale and the yields were determined spectroscopically. (Scheme 11).

SCHEME 11

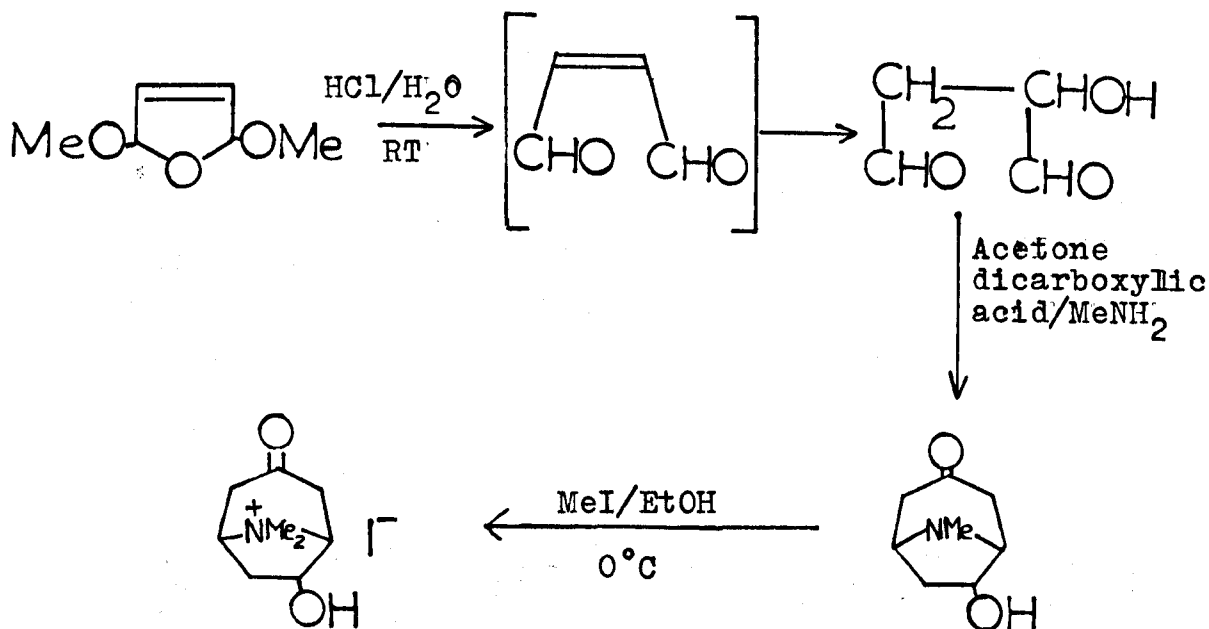


Tropinone can be prepared according to the method of Robinson (31) (Scheme 12) by the condensation of succindialdehyde with methylamine to give N-methyl-2,5-dihydroxytetrahydropyrrole, which on treatment with the calcium salt of acetone dicarboxylic acid gives the salt of tropinone-2,7-dicarboxylic acid, which can be hydrolysed and quaternised in the normal manner.

SCHEME 12



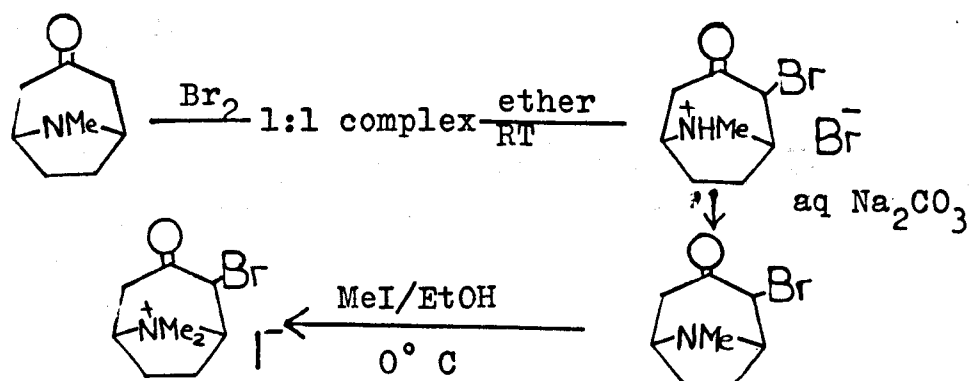
SCHEME 13



4-Hydroxytropinone was prepared from hydroxy-succindialdehyde, obtained by treatment of 2,5-dimethoxy-2,5-dihydrofuran with aqueous hydrochloric acid, acetone dicarboxylic acid and methylamine in 55% overall yield according to the method of Nedenskov and Clauson-Kaas (32). (Scheme 13).

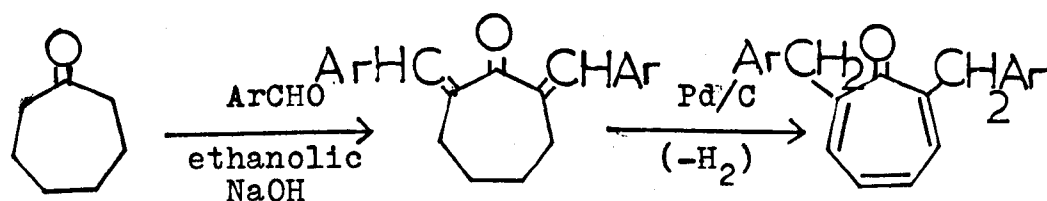
2-Bromotropinone methiodide was prepared from tropinone by treatment with bromine to yield a 1:1 complex, which, on standing at room temperature in ether for several days, decomposed to give 2-bromotropinone bromide in 92% yield. On treatment with aqueous sodium carbonate, 2-bromotropinone was liberated; this was converted to the methiodide in the usual way. (33) (Scheme 14).

SCHEME 14



2,7-disubstituted tropones have been prepared from suitable cycloheptanones by dehydrogenation over palladium-charcoal. Leonard, Miller and Berry (34) prepared a variety of 2,7-dimethylenecycloheptanones by condensation of cycloheptanone with various aromatic aldehydes according to the method of Cornubert, Joly and Strebel (35). On heating under reflux with 10% palladium-charcoal in triethylene glycol, 2,7-dibenzyltropones are formed in up to 57% yield. (Scheme 15)

SCHEME 15

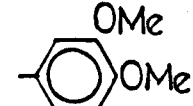


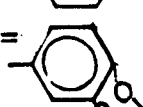
(XLII) Ar = -C₆H₅ (16%)

(XLIII) Ar = p-C₆H₄Me (57%)

(XLIV) Ar = p-C₆H₄iPr (12%)

(XLV) Ar = p-C₆H₄OMe (22%)

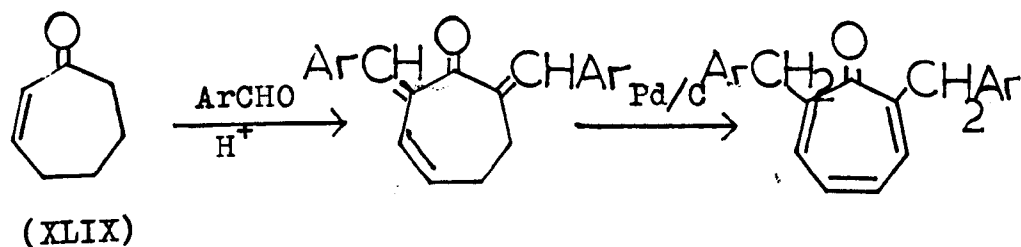
(XLVI) Ar = 

(XLVII) Ar = 

(XLVIII) Ar = p-C₆H₄NMe₂

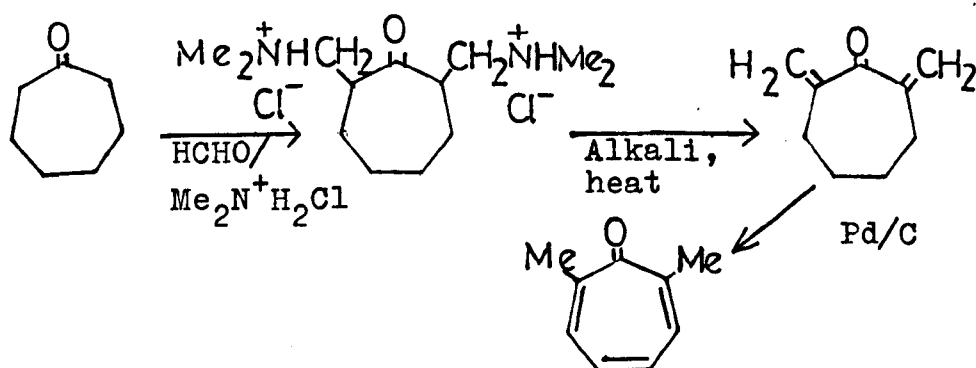
2,7-Dibenzyltropones have been prepared in a similar way by Treibs and Grossman (36) by treating cyclohept-2-enone (XLIX) with aromatic aldehydes under acidic conditions followed by treatment with palladium-charcoal. (Scheme 16).

SCHEME 16



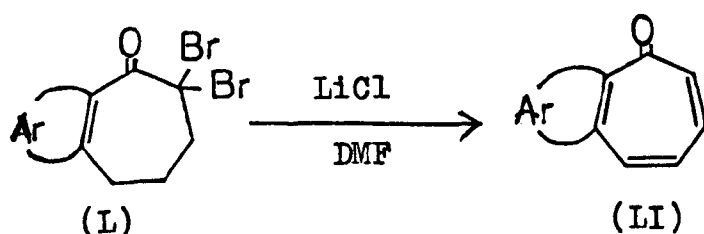
Mühlstädt (37) has reported the preparation of 2,7-dimethyltropone by hydrogenation of 2,7-dimethylenecycloheptanone, which is obtained from the product of a Mannich reaction between cycloheptanone and dimethylammonium chloride by treatment with alkali followed by heating. (Scheme 17).

SCHEME 17



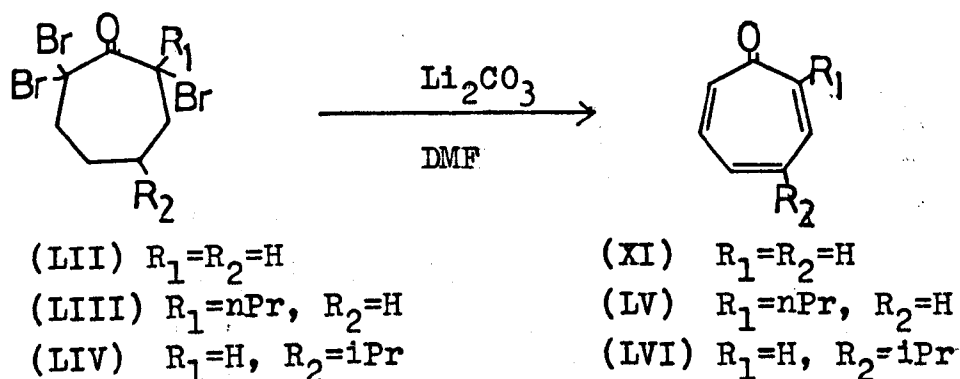
A general preparation of tropones was published in 1970 by Gurnos Jones (38). In 1968, Collington and Jones (39) published a route to tropones of type (LI) (where Ar represents an aromatic ring) by dehydrobromination of dibromo-compounds of the type (L) by treatment with lithium salts in boiling N,N-dimethylformamide (DMF).. (Scheme 18).

SCHEME 18.



In the case of compounds of the type (L), loss of two molecules of hydrogen bromide will lead to a troponoid compound. In the case of monocyclic systems, three molecules of hydrogen bromide must be eliminated. It was found (38) that treatment of 2,2,7-tribromocycloheptanone (LII) with 2 moles of lithium carbonate in boiling DMF gave tropone in 53% isolated yield (95% spectral yield). Similarly, 2-n-propyl-2,7,7-tribromocycloheptanone (LIII) gave the corresponding tropone (LV) in 75% yield. The method used for preparing 4-n-propyltribromocycloheptanone (LIV) led to the formation of two isomers which could not be separated; the crude mixture gave a 22% overall yield of 4-isopropyltropone (LVI) on treatment in the normal manner. The tribromoketones were prepared by treating the corresponding cycloheptanones with bromine in glacial acetic acid. (Scheme 19).

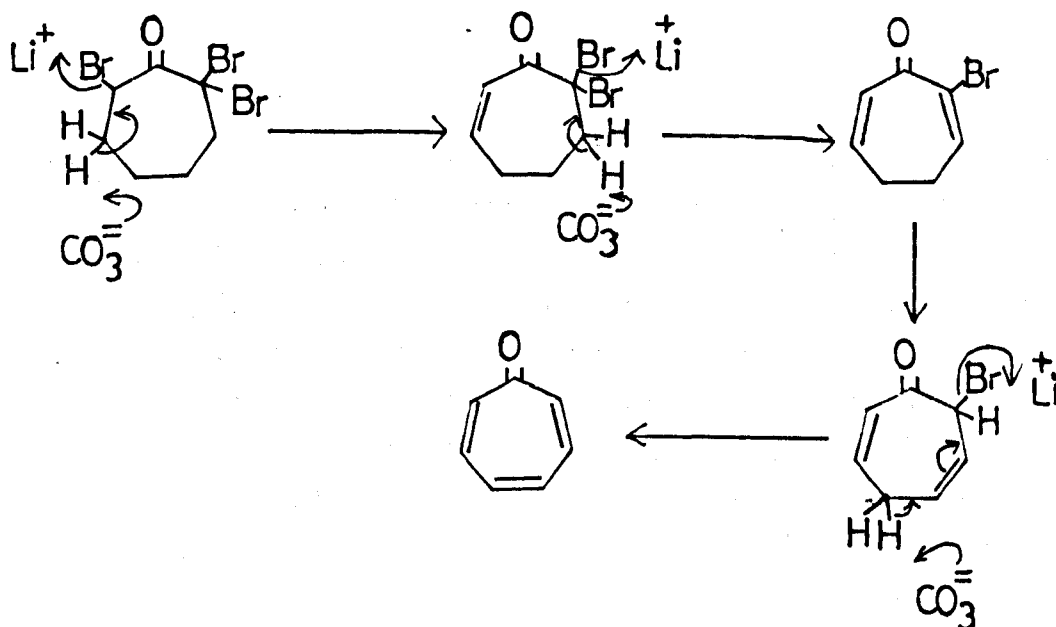
SCHEME 19



Collington and Jones (40) have published a paper in which they propose a mechanism for the dehydrobromination of 6,6-dibromobenz[b]cycloheptanone to benz[b]tropone, which can also be effected by this method. Extension of this mechanism to the case of

2,2,7-tribromocycloheptanone leads to the mechanism shown in Scheme 20.

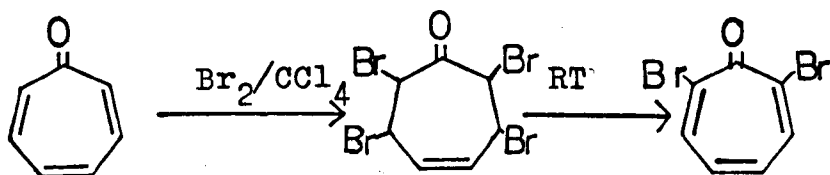
SCHEME 20



Finally, tropone can be prepared from cycloheptatriene by oxidation, using either chromium trioxide in pyridine or selenium dioxide, which give yields of 30-40%. (41,42).

The feature of tropone chemistry which was mainly responsible for the interest in this class of compounds was the tendency to show retention of type, a phenomenon usually associated with aromatic compounds. For example, halogens react with benzene to give substituted products rather than the addition compounds normally resulting from halogenation of unsaturated compounds; similarly, treatment of tropone with bromine in carbon tetrachloride leads eventually to a bromotropone. The initial product is 2,3,6,7-tetrabromocyclohept-4-enone, which loses hydrogen bromide on standing to yield 2,7-dibromotropone. (Scheme 21). (43,44).

SCHEME 21.



The carbonyl group does not display the normal reactions associated with this group; it is for example not possible to reduce tropone to cycloheptatriene using hydrazine hydrate in a conventional Wolff-Kishner reaction. Attempts to carry out such a reaction result in the isolation of 2-aminotropone, 2,7-disubstituted tropones showing no reaction with this reagent.

Dewar (1) recorded the absence of any of the usual ketonic properties in stipitatic acid; subsequent work has shown tropone to behave as a ketone, but requiring more drastic conditions than normal. For example, although tropone forms a semicarbazone and arylhydrazones, forcing conditions are required. (43).

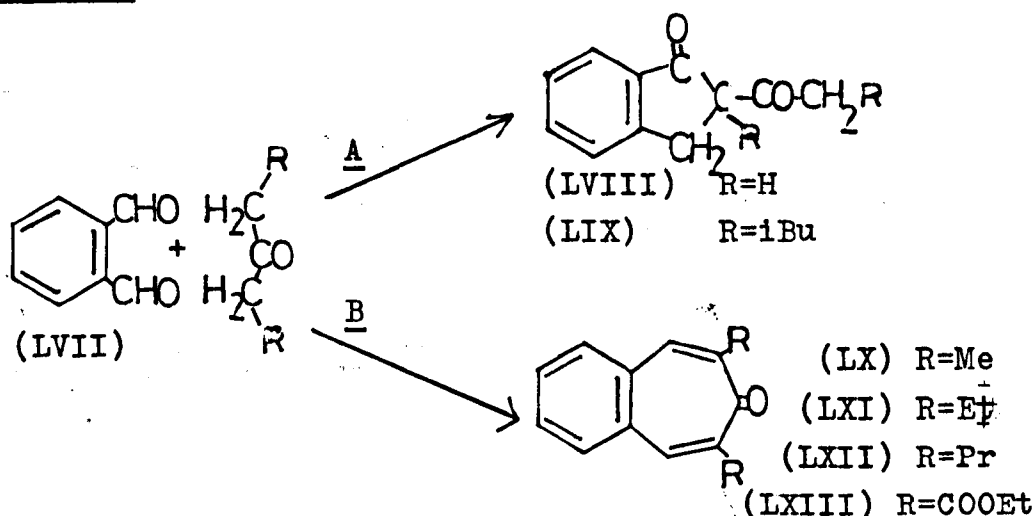
Bicyclic troponoid compounds.

In view of the potential aromaticity of the tropone system, a considerable amount of work has been carried out with the aim of synthesising compounds in which the tropone ring is fused onto another aromatic ring, in the hope that it will be possible to prepare an extensively delocalised system. It is interesting to note that a number of bicyclic tropones were prepared long before Dewar's proposed structure for stipitatic acid and the subsequent interest in the preparation

and properties of the monocyclic tropones. Furthermore, in contrast to the monocyclic field, the structures of the products were known.

The first example of a bicyclic tropone was due to Thiele and coworkers who, in 1909-1910, published a series of papers presenting the results of work on the condensation of phthalaldehyde (LVII) with suitable ketones. (Scheme 22).

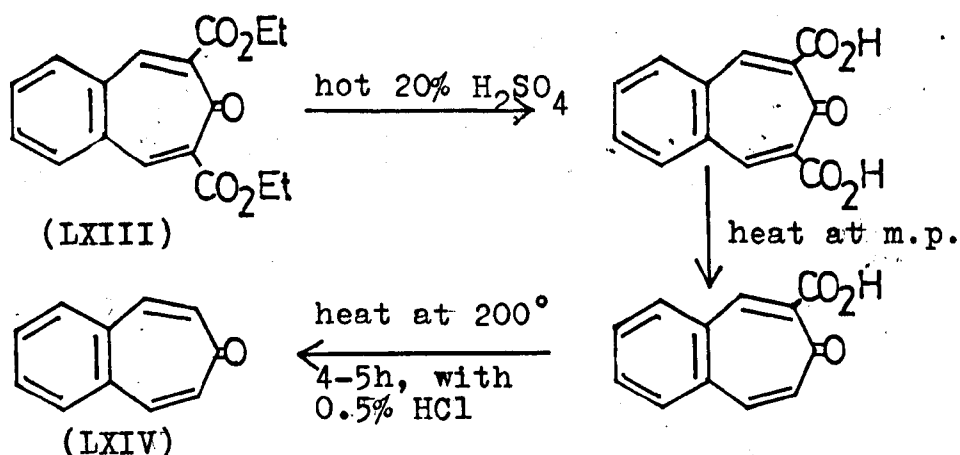
SCHEME 22.



Thiele initially studied the condensation under basic conditions of phthalaldehyde with acetone to give a hydrindone derivative (LVIII) (46). Three years later, Thiele and Schneider (47) reported that the condensation of phthalaldehyde with diethyl acetone-dicarboxylate gave, not a hydrindone derivative, but a dicarbethoxy benz[d]tropone (LXIII). Subsequently, Thiele and Weitz (48) reported that whether the reaction path is A or B (Scheme 22) depends on whether R- is a straight-chain or branched-chain alkyl group, the latter tending to lead to hydrindone derivatives.

Synthesis of the parent benz[d]tropone (LXIV) was effected via the dicarbethoxy benz[d]tropone (LXIII). Treatment of this with hot 20% sulphuric acid hydrolysed the ester groups to yield the dicarboxylic acid, which, on heating at its melting point decarboxylated to give the monobasic acid. Heating this at 200°C for four to five hours with 0.5% hydrochloric acid yielded the required benz[d]tropone. (Scheme 23).

SCHEME 23

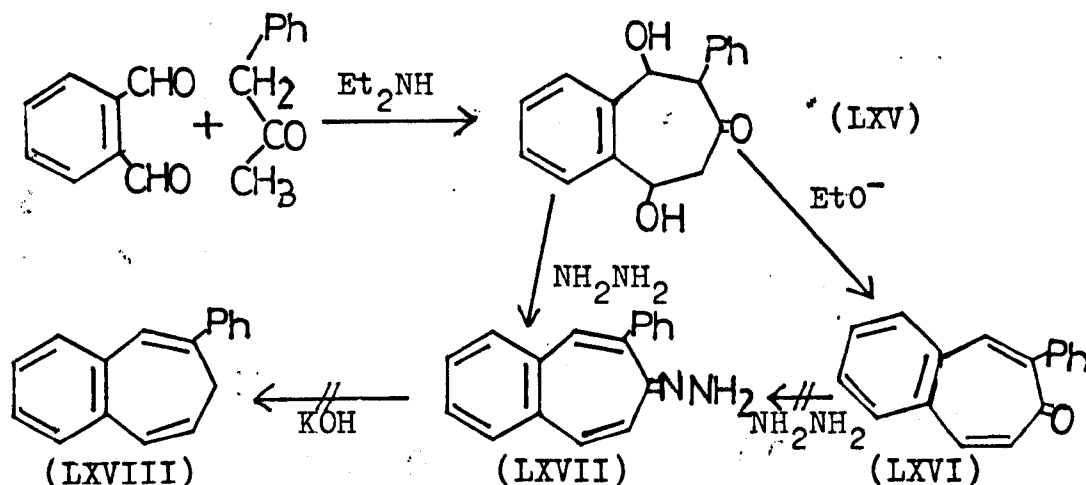


Thiele and Weitz reported that benz[d]tropone did not react to form an oxime or phenylhydrazine derivative; however, more recent workers have found that both of these reactions occur under normal conditions. (49).

In 1961 Davey and Gottfried (50) recorded a similar route to 6-phenylbenz[d]tropone (LXVI), involving the condensation of phthalaldehyde with benzyl methyl ketone in the presence of diethylamine. In this case the first product is not a tropone but a dihydro-dihydroxytropone (LXV). (Scheme 24). It was found that the benztropone (LXVI) did not react with hydrazine to form a hydrazone, but that the intermediate reacted to form the product that would be expected if the tropone showed the normal reaction of a ketone

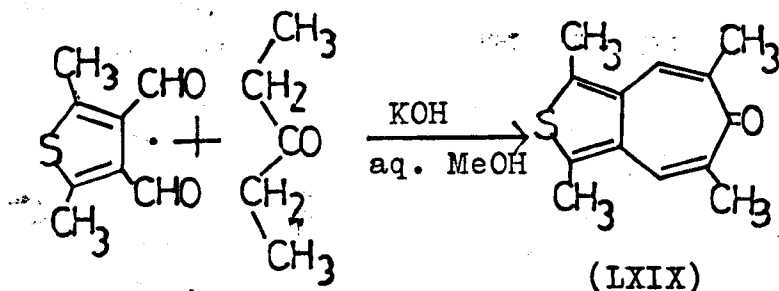
group under these conditions (LXVII). The condensation product could not, however, be converted into the cycloheptatriene (LXVIII). This failure of both ketones to undergo Wolff-Kishner reduction is further evidence of the stability of the tropone ring system.

SCHEME 24.



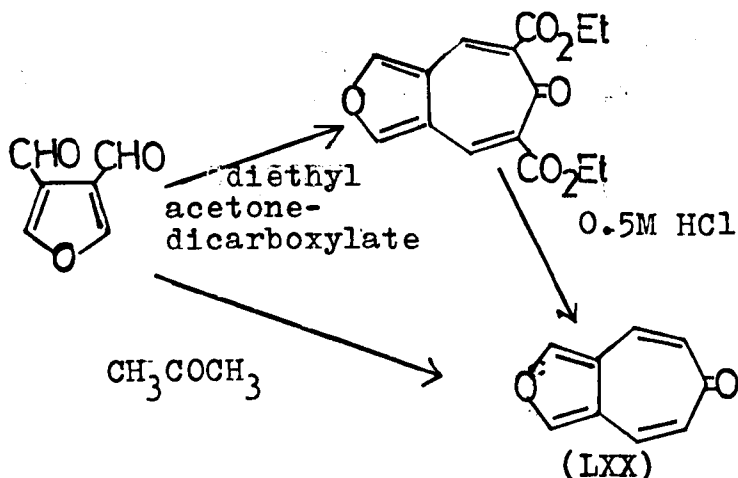
The method of Thiele and coworkers has been adapted for the synthesis of a variety of thieno- and furo-tropones. In 1967 Winn and Bordwell (51) reported the synthesis of 2,4,6,8-tetramethyl-5H-cyclohepta[3,4-d]thiophen-5-one (LXIX) in 43% yield from the condensation of 2,5-dimethylthiophen-3,4-dialdehyde with pentan-3-one. (Scheme 25).

SCHEME 25



In the same year Cook and Forbes (49) reported the synthesis of furo[4,5-c]tropone (LXX) by two routes, both starting from furan-3,4-dialdehyde. (Scheme 26).

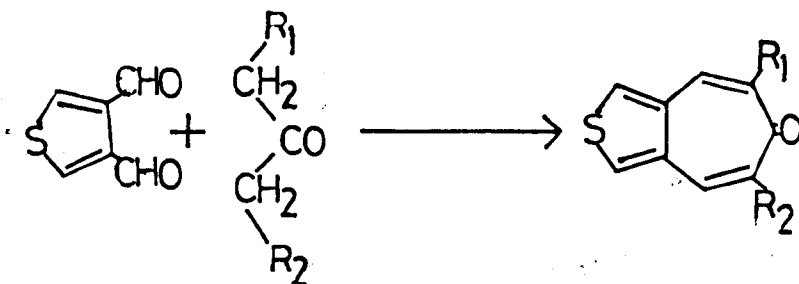
SCHEME 26



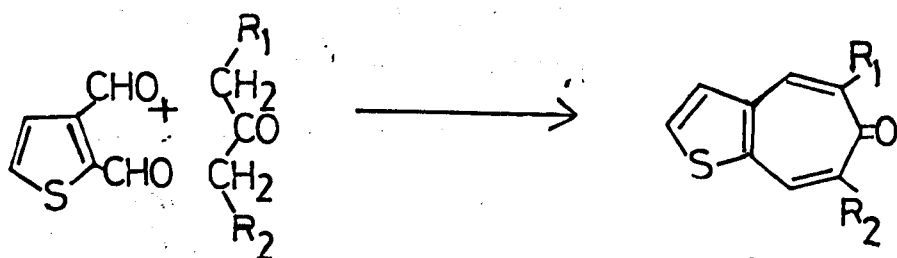
Direct condensation with acetone in the presence of sodium hydroxide in aqueous ethanol yielded the furotropone in 38% yield. Alternatively, heating the dialdehyde with diethyl acetonedicarboxylate with a trace of piperidine in benzene for two hours gave 2,7-dicarbethoxyfuro[4,5-c]tropone in 74% yield, which, on heating for three hours in a sealed tube at 175-180°C with 0.5M HCl, decarboxylated to give a 7% yield of the tropone.

Guillard and Fournari (52) have used this method to prepare thieno[4,5-b]tropones and thieno[4,5-c]-tropones.. (Scheme 27).

SCHEME 27



	R_1	R_2	Yield		R_1	R_2	Yield
LXXI	H	H	16%	LXXV	Me	Me	84%
LXXII	Me	H	48%	LXXVI	COOEt	COOEt	44%
LXXIII	OH	H	19%	LXXVII	C_6H_5	C_6H_5	25%
LXXIV	OMe	H	49%				

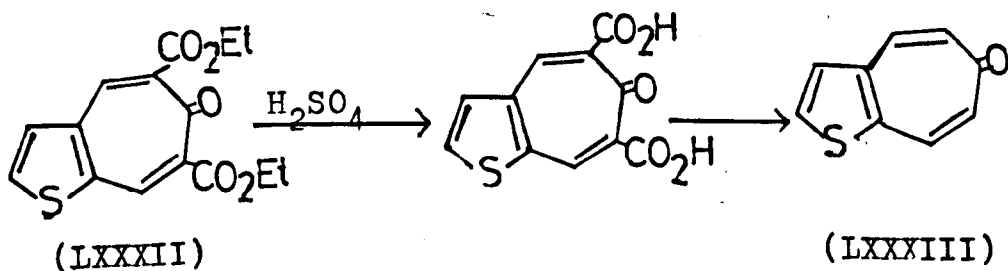


	R ₁	R ₂	Yield ^a
(LXXVIII)	Me	H	57%
(LXXIX)	OH	H	19%
(LXXX)	Me	Me	77%
(LXXXI)	Ph	Ph	44%
(LXXXII)	COOEt	COOEt	76%

It was found that it was not possible to prepare the parent thieno[4,5-b]tropone by direct condensation of acetone with thiophen-2,3-dialdehyde. However, hydrolysis of the dicarbethoxy tropone (LXXXII) with sulphuric acid, followed by decarboxylation, gave the required compound (LXXXIII) in 14% overall yield from the dialdehyde. (Scheme 28).

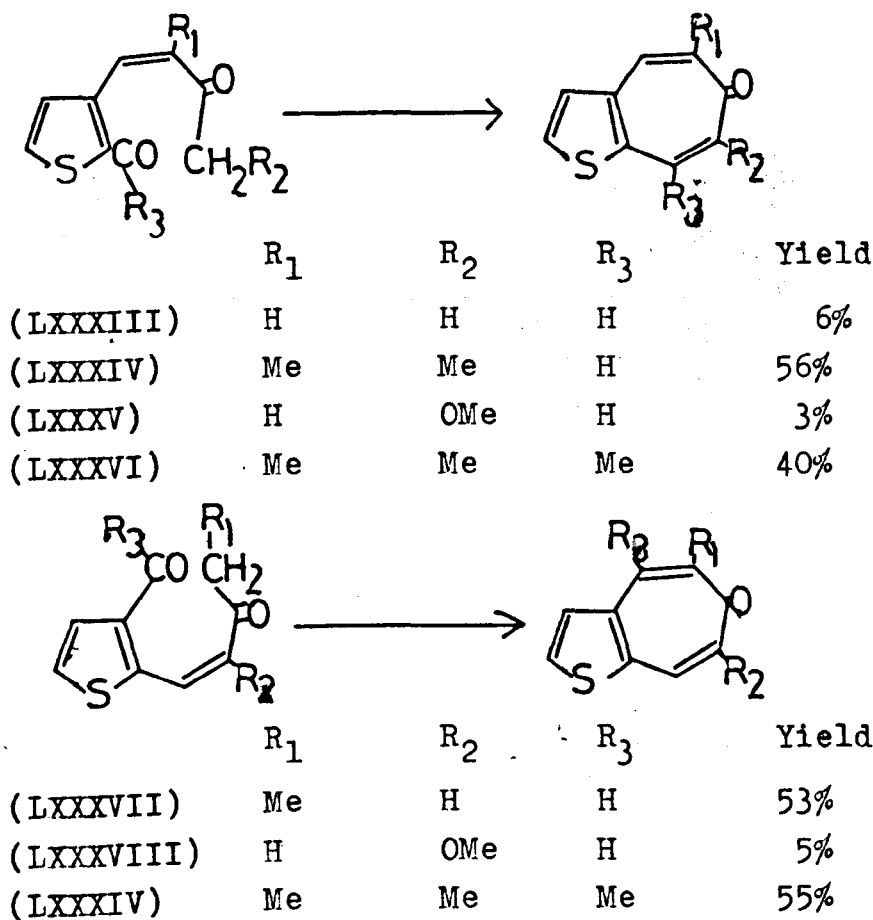
The reaction between thiophen-2,3-dialdehyde and butanone can in principle lead to either the 5-methyl or the 7-methyl thieno[4,5-b]tropone. It was found however that the compound having the methyl group in the 5 position was the major product, and that it was not possible to prepare the compound with

SCHEME 28



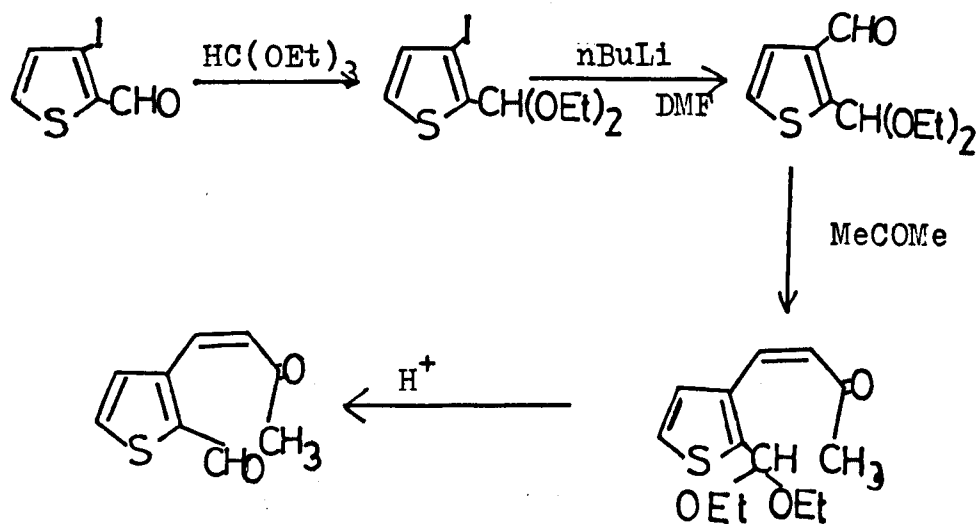
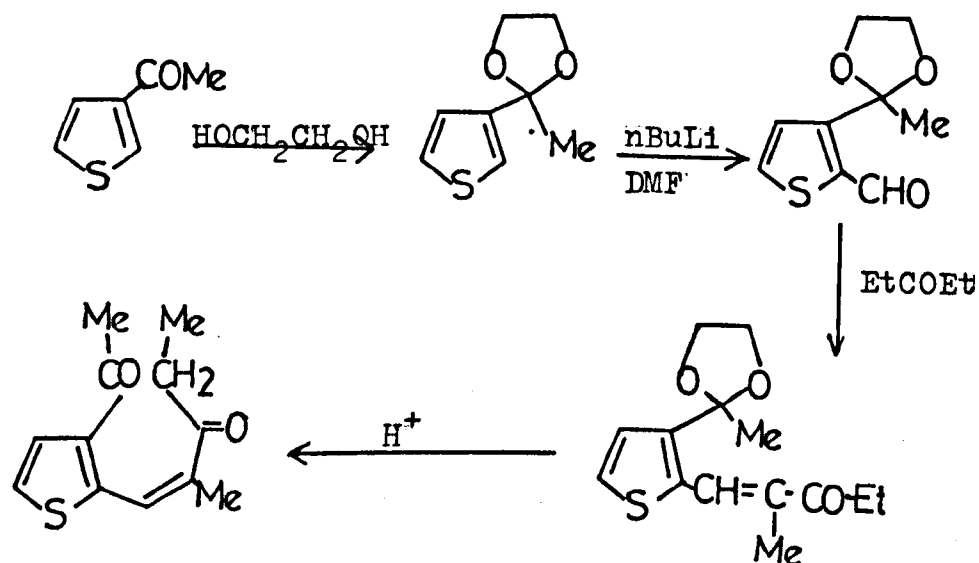
the methyl group in the 7 position by this method. Guillard and Fournari devised another route which lead unambiguously to 7-methylthieno[4,5-b]tropone. (Scheme 29).

SCHEME 29



The reactions in Scheme 29 were all carried out under acidic conditions in anhydrous ether at high dilution. Although in principle many of these compounds can be prepared by either of the routes shown in Scheme 29, it was found that in some cases only one of the precursors gave the required product. For example, the unsubstituted thieno[4,5-b]tropone (LXXXIII) can be obtained only by the first method shown in this scheme.

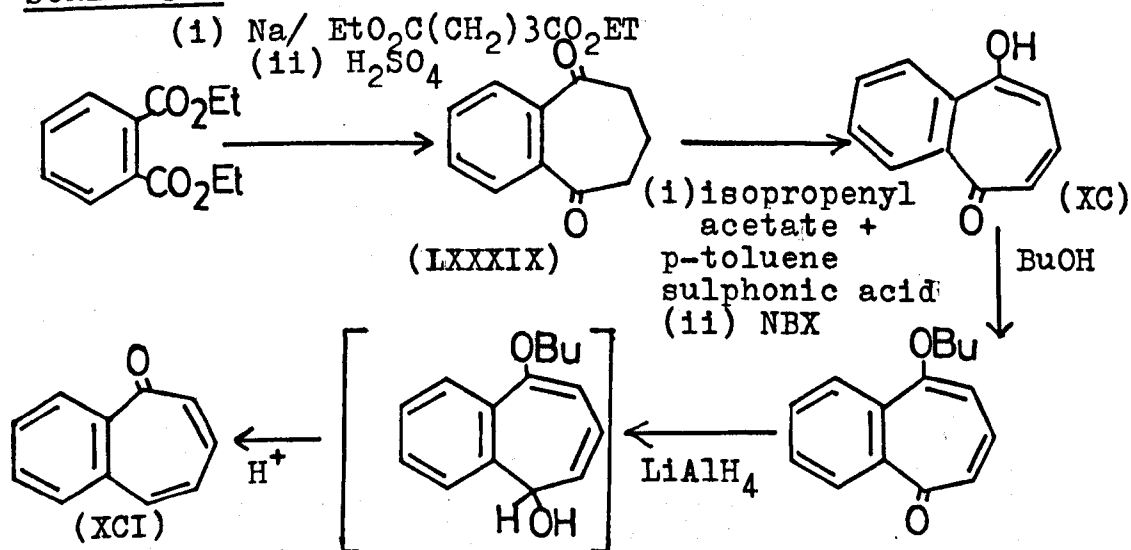
SCHEME 30



The synthesis of the precursors starts from a thiophen compound having a carbonyl group on either position 2 or position 3, which can be protected by acetal or ketal formation whilst the remainder of the molecule is built up. Two such syntheses are illustrated in Scheme 30. The starting materials are available by literature methods.

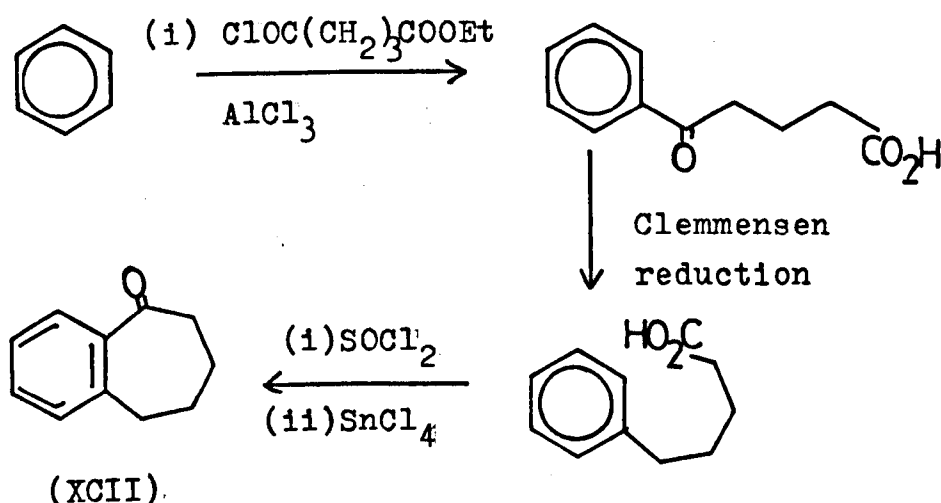
The synthesis of benz[2,3]tropone (XCI) was first achieved in 1957 (53). The method used involved starting with a benztropolone (XC) and oxidising the hydroxy group to a ketone and reducing the carbonyl to a hydroxyl group which is eliminated during work-up. This is effected by forming a butyl ether on treatment with butanol, reduction of the carbonyl group to an alcohol using lithium aluminium hydride, followed by treatment with acid which brings about the elimination of a molecule of butanol to liberate benz[2,3]tropone. The benztropolone is prepared from benzcycloheptadione (LXXXIX) in 29% yield (54), which is prepared in 20% yield from diethyl phthalate (55). The conversion of benztropolone to benztropone was achieved in 69% overall yield. (Scheme 31).

SCHEME 31



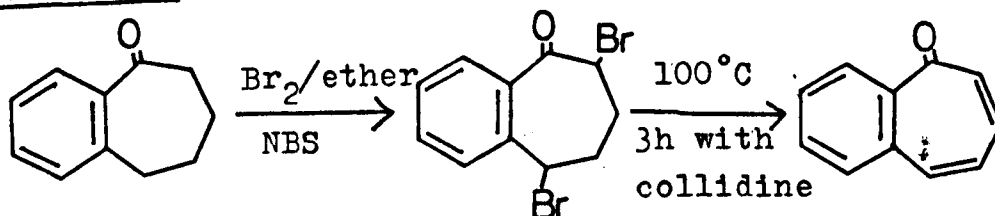
In 1959, Buchanan and Lockhart (56) reported a more convenient synthesis of benz[2,3]tropone from benz[2,3]cycloheptanone (XCII) which could be prepared by acylation of benzene, followed by Clemmensen reduction and internal Friedel-Crafts reaction. (57). (Scheme 32).

SCHEME 32



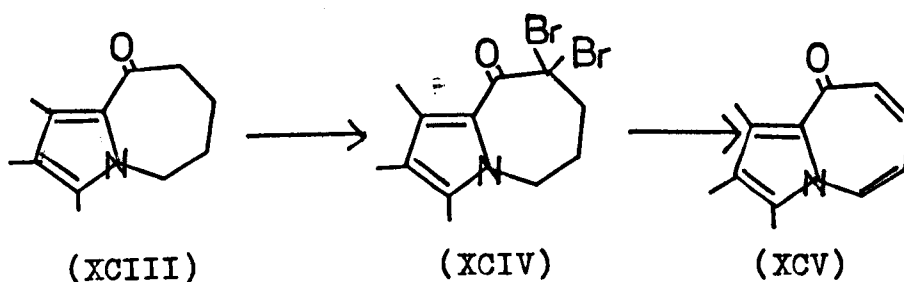
Bromination of the bicyclic ketone (XCII) with bromine in ether (58) gave a 94% yield of 6-bromo-benz[2,3]cycloheptanone which, on treatment with N-bromosuccinimide, yielded 6,9-dibromobenz[2,3]cycloheptanone. On heating at 100°C for three hours with collidine, the dibromo-compound lost two molecules of hydrogen bromide to give a 63% yield of benz[2,3]tropone (XCI)

SCHEME 33



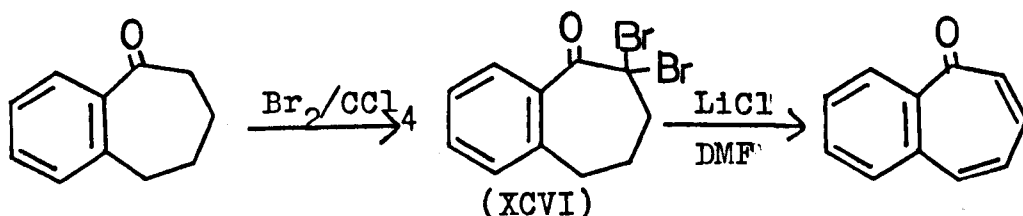
In 1968, Collington and Jones (59,60) reported that cyclic ketones of the type (XCIII) could be brominated to yield the dibromo-ketone (XCIV) which, on treatment with lithium chloride in boiling DMF gave a good yield of the corresponding azepinone (XCV). (Scheme 34).

SCHEME 34



This work was subsequently extended (61) to the synthesis of benz[2,3]tropone. Treatment of benz[2,3]cycloheptanone with 2 moles of bromine in carbon tetrachloride yielded 6,6-dibromobenz[2,3]cycloheptanone (XCVI) quantitatively. Treatment of this with anhydrous lithium chloride in boiling DMF gave a 92% yield of benz[2,3]tropone. (Scheme 35).

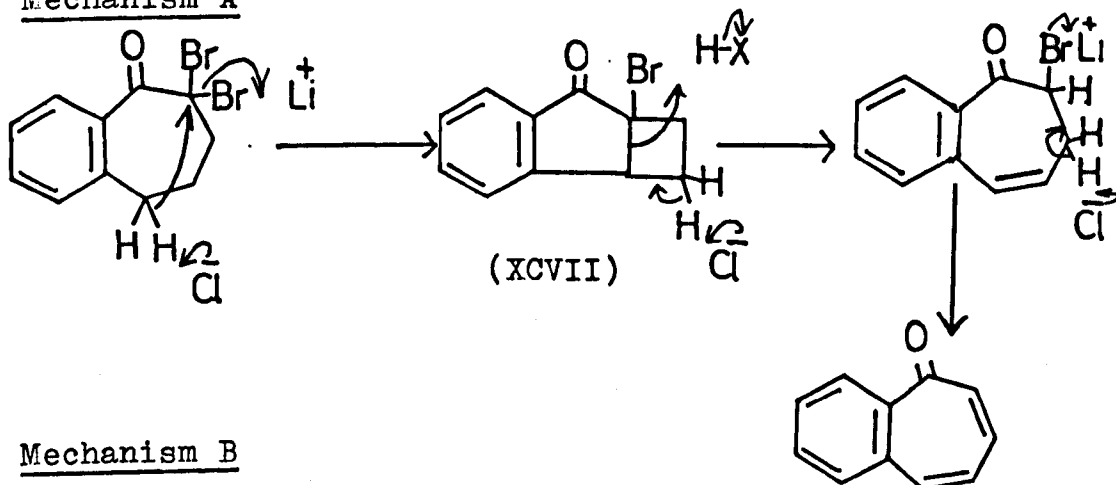
SCHEME 35



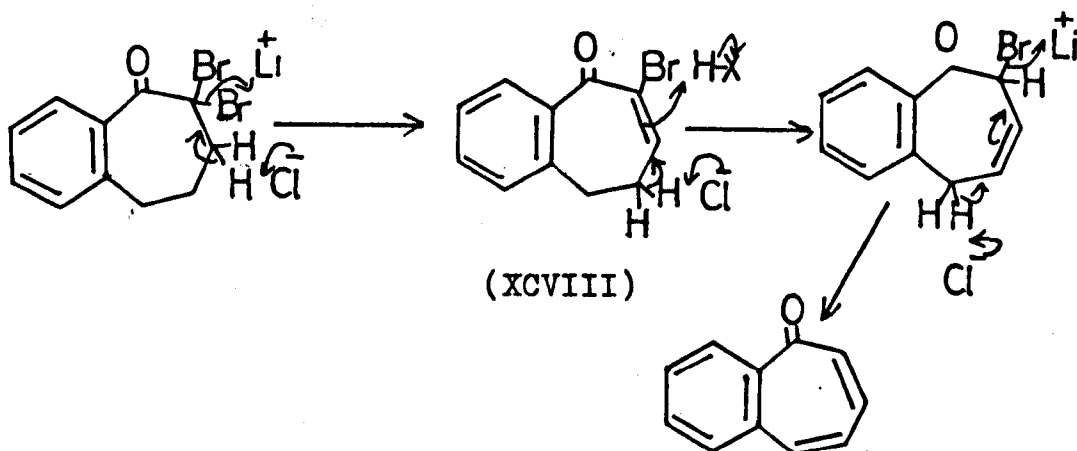
It was thought that one of two mechanisms was responsible for this reaction. (Scheme 36). Collington and Jones (62) prepared a tricyclic ketone having a molecular formula corresponding to (XCVII), although it was not possible to be certain on which bridgehead position the bromine was situated; however, on boiling this compound with lithium chloride in DMF, it was recovered unchanged. The proposed intermediate for mechanism B (XCVIII) was also prepared, and on treatment with lithium chloride in boiling DMF was converted to benz[2,3]tropone, indicating that mechanism B is probably the correct one.

SCHEME 36

Mechanism A

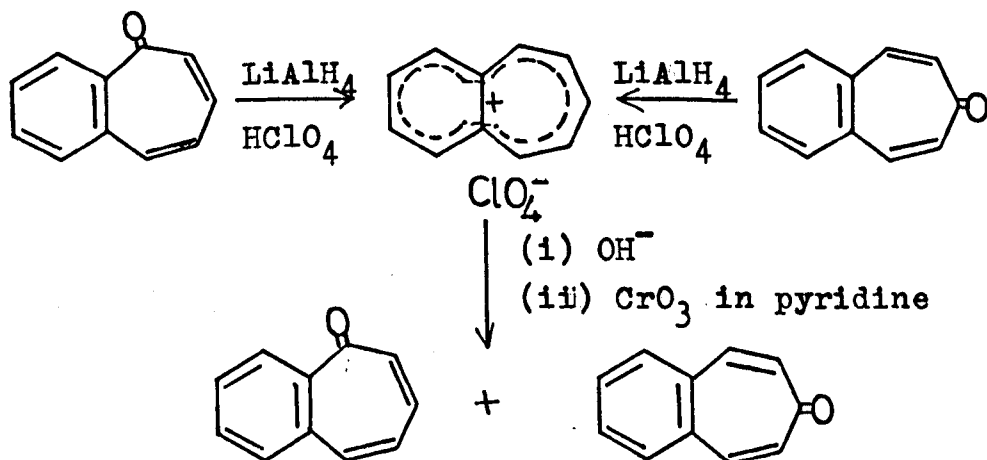


Mechanism B



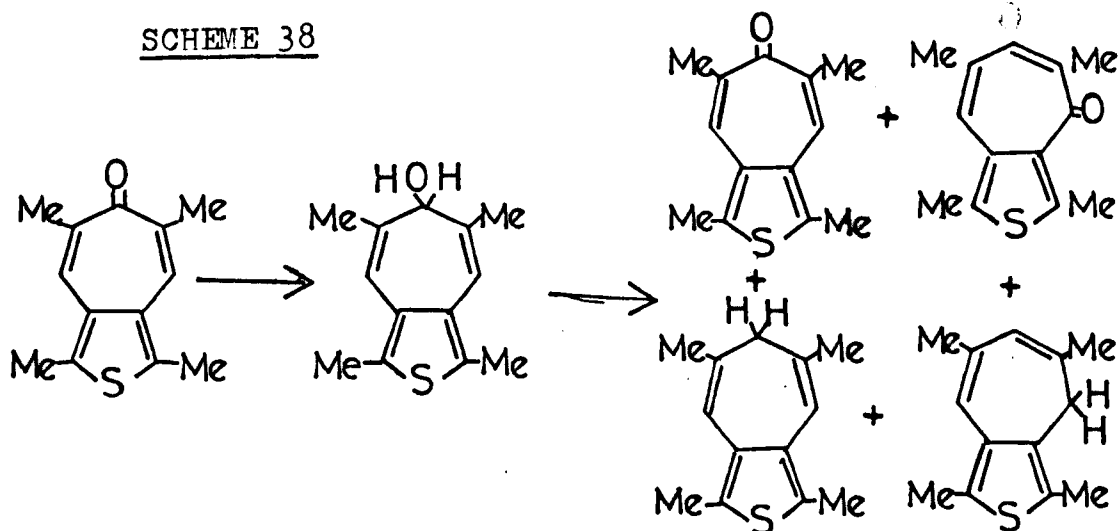
It has been reported that interconversion between benz[2,3]tropone and benz[4,5]tropone is possible via benztropylium salts. In 1957, Eschenmoser and co-workers reported that lithium aluminium hydride reduction of benz[2,3]tropone yielded the corresponding alcohol, which, on treatment with a strong acid such as perchloric acid, gave a benztropylium salt. (53) Treatment of this with base, followed by oxidation with chromium trioxide in pyridine yielded a mixture of benz[2,3]tropone and benz[4,5]tropone. In 1958, Meuche, Strauss and Heilbronner (63) reported the corresponding reaction sequence starting from benz[4,5]tropone. (Scheme 37).

SCHEME 37



In 1969, Ginesina and El'tsov (64) reported a similar interconversion in the thiophen series; reduction of 2,4,6,8-tetramethyl-5H-cyclohepta[3,4-d]-thiophen-5-one led to the corresponding alcohol which, on standing at room temperature in carbon tetrachloride or acetonitrile, disproportionates into a mixture of starting material, the isomeric structure having the carbonyl group in the 7 position, and reduced analogues. (Scheme 38).

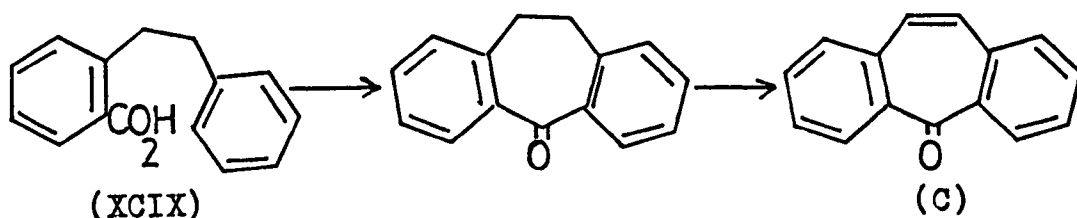
SCHEME 38



Polycyclic troponoid compounds.

Dibenzo[2,3-6,7]tropone (C) was prepared by Treibs and Klinkhammer (65) from 2-(2-phenylethyl)-benzoic acid (XCIX) by an internal Friedel-Crafts reaction followed by photo-oxidation by bromine. (Scheme 39).

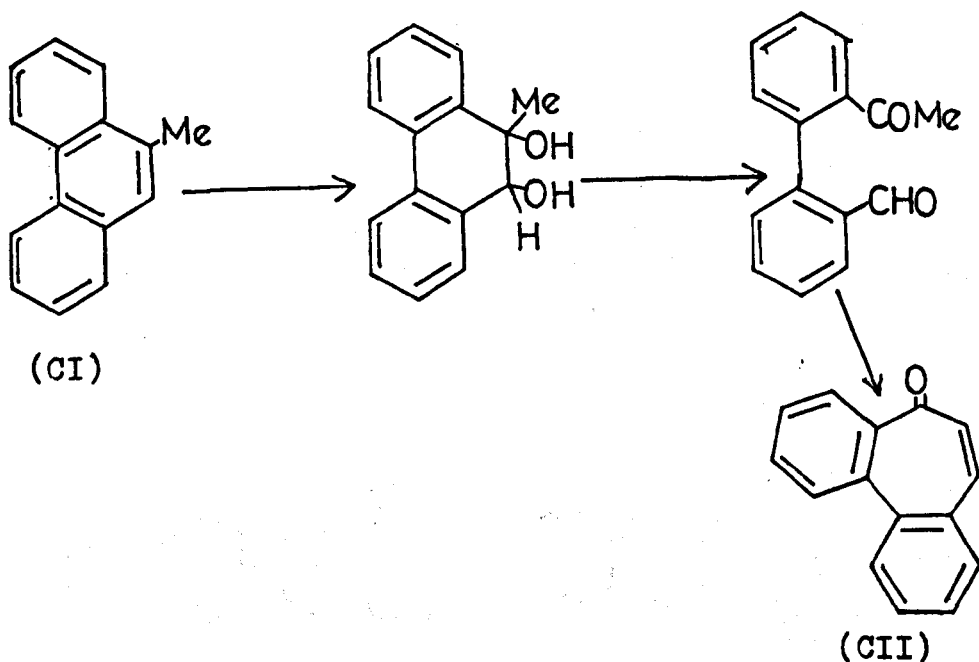
SCHEME 39



G. Berti (66,67) has reported a synthesis by means of an internal Friedel-Crafts reaction on *cis*-stilbene-2-carboxylic acid, which gives a 33% yield.

Dibenzo[2,3-4,5]tropone (CII) has been prepared by Buchanan and coworkers (68) by treatment of 9-methylphenanthrene (CI) with osmium tetroxide and pyridine in benzene to give 9,10-dihydroxy-9,10-dihydro-9-methylphenanthrene. Oxidation of this with lead tetraacetate causes cleavage of the 9-10 bond

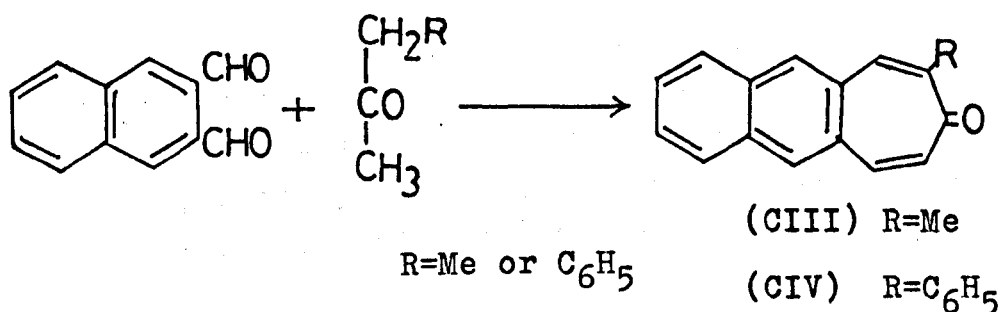
SCHEME 40



and recyclization yields the required product. (Scheme 40).

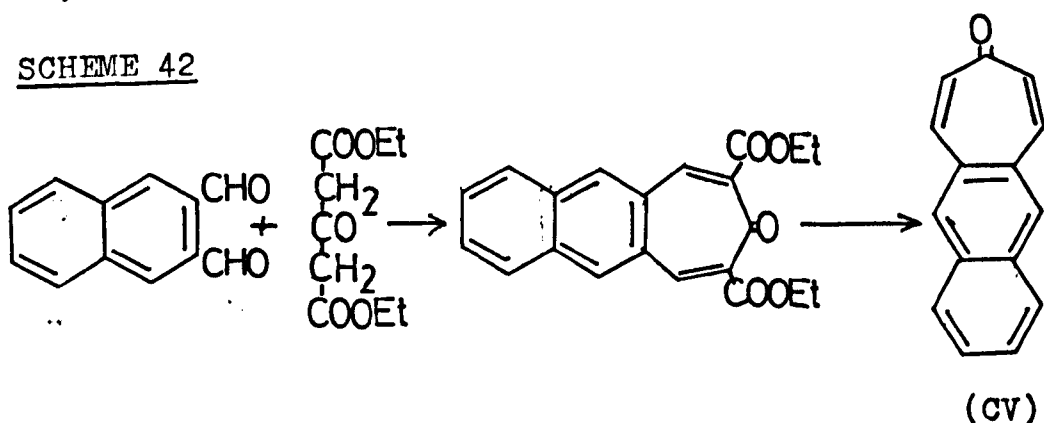
Naphtho[4,5-b]tropones have been prepared by the condensation of suitable carbonyl compounds with naphthalene-2,3-dialdehyde using the methods of Thiele and coworkers (47, 48). The 7-methyl and 7-phenyl derivatives have been prepared in one step by Ried and Schweneke (69) and Treibs and Lippmann(70) respectively. (Scheme 41).

SCHEME 41.



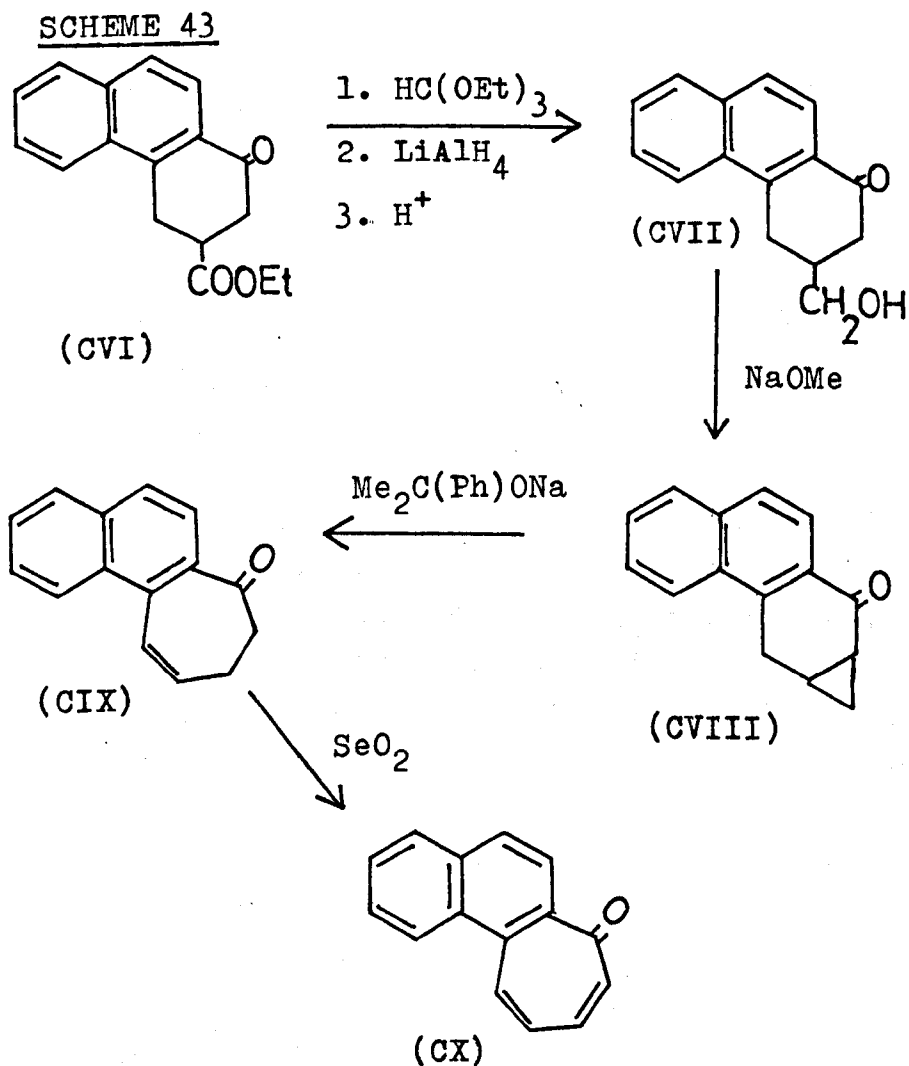
The parent compound cannot be obtained by direct condensation with acetone. Naville, Strauss and Heilbronner (71) have prepared it by condensation of the dialdehyde with diethyl acetonedicarboxylate followed by treatment with methanolic potassium hydroxide which causes first hydrolysis and then decarboxylation to yield the parent naphtho[4,5-b]tropone (CV). (Scheme 42).

SCHEME 42



To date, no compounds containing the naphtho[2,3-b]tropone skeleton have been reported in the literature.

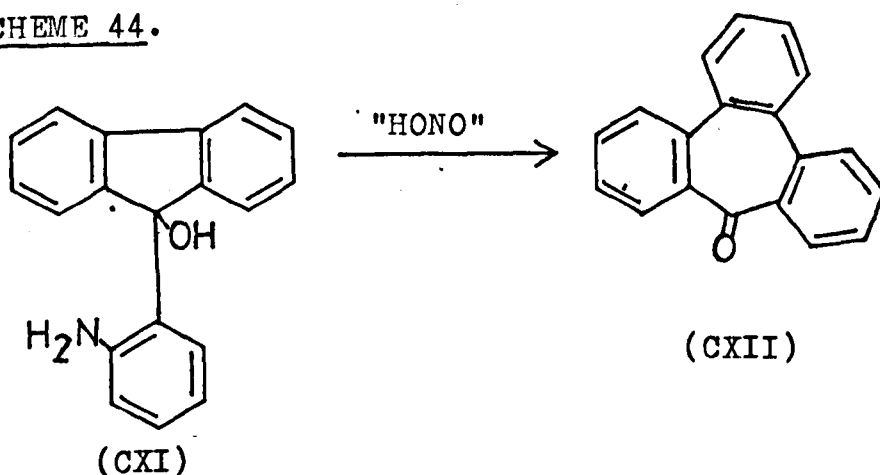
Julia, Bonnet and Schaeppi (72) have reported the synthesis of naphtho[2,3-a]tropone starting from 2,3,4-trihydro-3-carbethoxy-1H-phenanthrene-1-one (CVI). Protection of the carbonyl group by ketal formation followed by lithium aluminium hydride reduction of the ester group leads to the 3-hydroxymethyl compound (CVII). Treatment of this with base leads to the cyclopropane derivative (CVIII), which, on treatment with the sodium salt of dimethylphenylcarbinol gives 8,9-dihydro-7H-naphtho[2,3-b]cyclohepten-7-one (CVIX), which yields the required tropone (CX) on oxidation with selenium dioxide. (Scheme 43).



Neither 7H-cyclohepta[2,3-a]naphthalene-7-one nor naphtho[4,5-a]tropone has been reported in the literature.

Tribenz[2,3-4,5-6,7]tropone (CXII) has been prepared by Stiles and Libbey (73) by treatment of 9-o-aminophenyl-9-fluorenol (CXI) with nitrous acid. (Scheme 44).

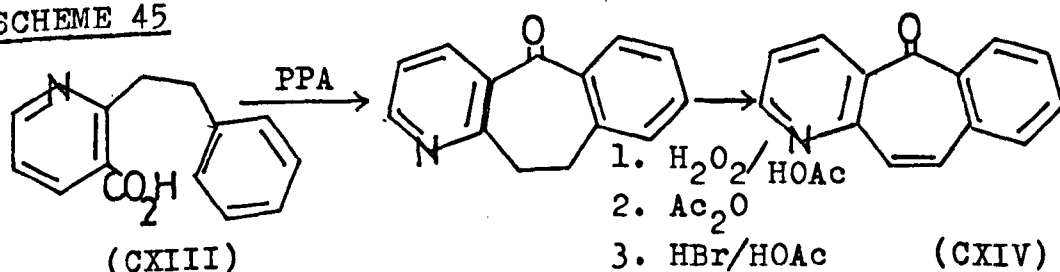
SCHEME 44.



To date, no examples of compounds containing a tropone ring fused to anthracene, phenanthrene or higher hydrocarbons have been reported in the literature.

Some work has been carried out on compounds containing a tropone ring fused to a heterocyclic system containing nitrogen. For example, 1-aza-5H-dibenz[a,d]cyclohepten-5-one (CXIV) has been prepared by cyclic dehydration of 2-phenethylnicotinic acid (CXIII) using polyphosphoric acid (PPA), followed by treatment with hydrogen peroxide in acetic acid to form the N-oxide, with subsequent aromatisation with acetic anhydride followed by hydrogen bromide and acetic acid (74). (Scheme 45). The 2-aza analogue has been prepared in a similar manner. An alternative method of introducing the final double bond into the cyclised material is treatment with N-bromo-succinimide, followed by dehydrobromination with triethylamine, which gives the tropone in 55% overall yield (75). These compounds have been shown to be antihistamine agents.

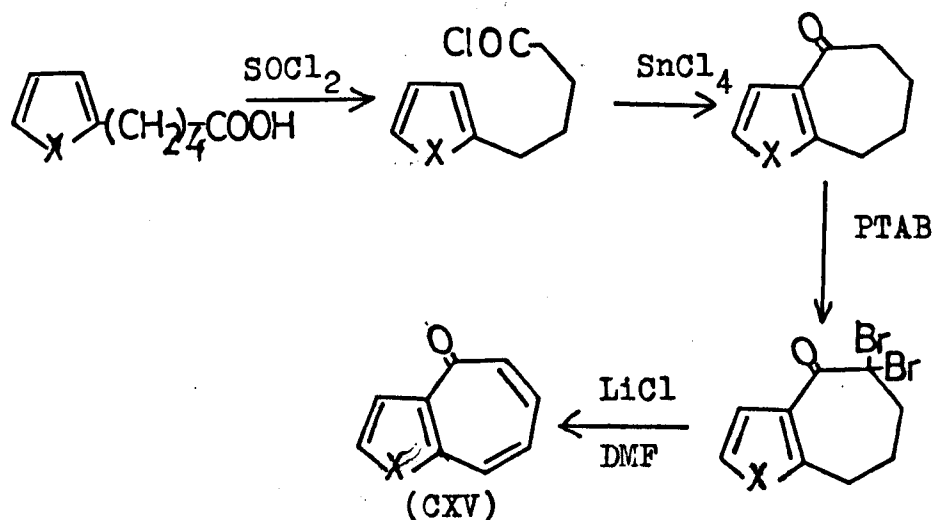
SCHEME 45



DISCUSSION



In 1969, Collington and Jones (59,60) reported the synthesis of benz[b]tropone in 92% yield from an α,α -dibromoketone with two moles of lithium chloride in boiling N,N-dimethylformamide (DMF). In 1970, Jones (38) reported that this method could also be used to prepare a variety of monocyclic troponoid compounds. Although various thieno- and furotropones have been reported in the literature (49, 51, 52, 63), no examples of the type (CXV) (X=O or S) have appeared; it was felt that it should be possible to prepare compounds of this type by the general method of preparing 5-arylpentanoic acids, causing them to undergo internal Friedel-Crafts reactions to yield bicyclic ketones which, on treatment with phenyl trimethylammonium tribromide (PTAB) in tetrahydrofuran (THF) should yield suitable precursors for double dehydrobromination reactions of the type described by Collington and Jones. (Scheme 46).

SCHEME 46





For thiophen and furan to display aromatic properties, they must have 6π electrons. For this to be possible, the heteroatoms in these compounds must each donate one lone pair to the system. That this occurs can be seen by comparing the dipole moment of thiophen (0.52D) with that of tetrahydrothiophen (1.87D), and that of furan (0.71D) with that of tetrahydrofuran (1.68D). Both thiophen and furan are electron rich systems in comparison with benzene, and so would be expected to undergo electrophilic substitution reactions more readily than benzene, as is in fact found to be the case.

Although molecular orbital calculations (76) show that the electron densities round the thiophen ring are greater than 1 for each carbon atom, they seem to indicate that electrophilic attack should take place at C3 and C4, as the electron densities are higher for these positions than for C2 and C5. It is found in practice that electrophilic substitution occurs predominantly (and often exclusively) at C2, or, for 2-substituted thiophens, at C5. Localisation energies are a better guide than electron densities to the position at which electrophilic attack will occur, but even these are not completely reliable, for it is found that the relative proportions of 2- and 3-alkyl thiophens formed under Friedel-Crafts conditions vary from 1:1 to 3:1 depending on the Lewis acid catalyst used.

	1.073		163.3
	1.022		160.7
π -Electron densities		Localisation energies	
		(k cal/mole)	

Furan is similarly more reactive than benzene in electrophilic substitution reactions, although the susceptibility of the ring to cleavage by acids with subsequent polymerisation means that such reactions have to be carried out under conditions in which the compound is not allowed to come into contact with warm aqueous acid. Molecular orbital calculations (76) of electron density predict that electrophilic attack should occur at C3 or C4, but, as for thiophen, this is found to be the case only when both α positions are already substituted. Calculations of localisation energy (76) for furan indicate that attack at C2 or C5 is energetically more favourable than attack at C3 or C4.

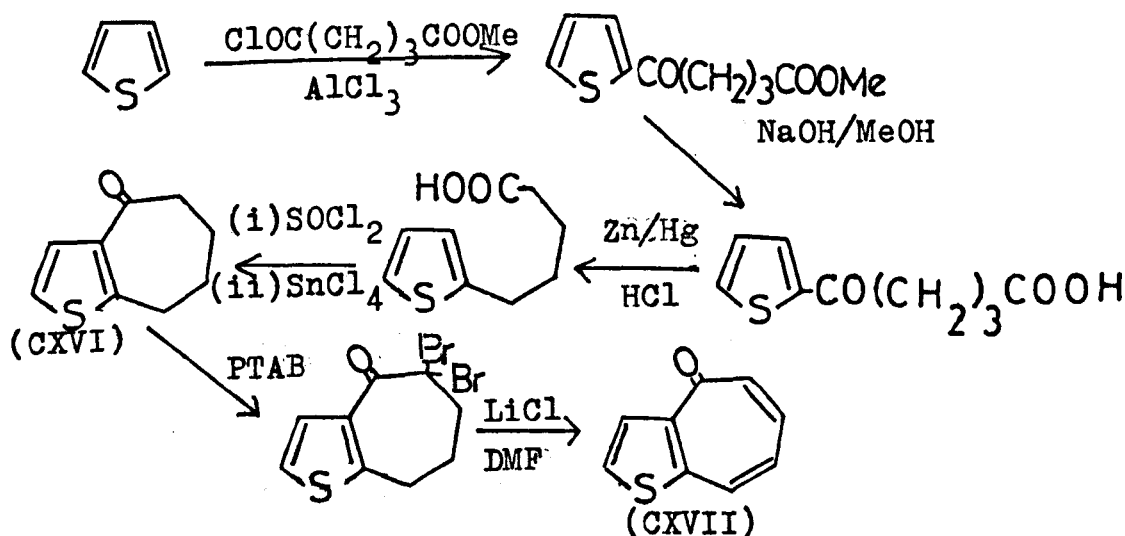
	1.083		235.7
	1.017		135.6
π -Electron densities		Localisation energies	
		(k cal/mole)	

Measurements of the resonance stabilisation energy of furan (25 kcal/mole) (76,77) and thiophen (30 kcal/mole) (76) show that both compounds are less aromatic in character than benzene (36 kcal/mole). Furan in fact behaves in many respects as a diene, in particular in its readiness to participate in Diels-Alder reactions. Thiophen tends to display much less diene character than furan, but it has recently been reported in the literature (78) that thiophen undergoes a Diels-Alder reaction with dicyanoacetylene.

The readiness of thiophen and furan to undergo electrophilic substitution makes possible the use of milder Lewis acid catalysts for Friedel-Crafts reactions than are required for benzene.

Cagniant and Deluzarche (79) have reported a synthesis of 5,6,7,8-tetrahydro-4H-cyclohepta[3,2-b]-thiophen-4-one (CXVI) starting from thiophen; acylation with methyl glutaryl chloride using anhydrous aluminium chloride in carbon disulphide, followed by hydrolysis of the ester group and subsequent reduction of the carbonyl group using zinc amalgam and hydrochloric acid yield 5-(thienyl-2)pentanoic acid. Treatment of this with thionyl chloride at room temperature was reported to give the acid chloride in good yield, which on treatment with anhydrous stannic chloride in carbon disulphide gave the required bicyclic ketone. Bromination of this compound using PTAB, followed by treatment with lithium chloride in boiling DMF should have led to the parent thieno[b]tropone (CXVII). (Scheme 47).

SCHEME 47



It was found that 4-(thienoyl-2)butyric acid could be more conveniently prepared using a modification of the method of Yur'ev and Elyakow (80) for the preparation of thienyl ketones. Heating monomethyl glutarate with anhydrous silicon tetrachloride in boiling benzene until no more HCl was evolved led to the formation of a silicate; this could be used to acylate thiophen using stannic chloride as a catalyst. The carbonyl group of the acid obtained from hydrolysis of the product of the acylation reaction was reduced using hydrazine hydrate according to the method of Badger, Rodda and Sasse (81). However, attempts to isolate the acid chloride were unsuccessful; treatment of the acid with thionyl chloride at room temperature, using either equimolar proportions or a 100% excess failed to produce any material which could be distilled. Carrying out the reaction in boiling anhydrous ether, as reported by Cagniant and Cagniant (82) for the preparation of a similar compound, also led to a mixture from which none of the desired product could be isolated. The residue from distillation attempts had bands in the carbonyl region of the infra-red spectrum at 1740 and 1810 cm^{-1} ; the failure of the mixture to distil excluded the possibility that these bands were due to the presence of a mixture of the acid chloride and free acid. A spacing of 60 cm^{-1} is indicative of an anhydride, suggesting that the reaction mixture might contain the acid chloride and free acid, which, on heating, eliminate HCl to form the anhydride. In an attempt to ensure that all the acid was converted to the acid chloride before attempting the distillation, the acid was boiled under reflux with two moles of thionyl chloride in anhydrous ether until the i.r. spectrum showed virtually no trace of starting material. However, no product could be distilled from the mixture obtained under these conditions.

In their synthesis of 5,6,7,8-tetrahydro-2-methyl-4H-cyclohepta[3,2-b]thiophen-4-one, Cagniant and Cagniant (82) stated that the internal Friedel-Crafts reaction was carried out using the crude acid chloride. Attempts to prepare 5,6,7,8-tetrahydro-4H-cyclohepta[3,2-b]thiophen-4-one using the crude product from the reaction between 5-(thienyl-2)pentanoic acid and thionyl chloride were, however, unsuccessful.

Attempts to effect this internal Friedel-Crafts reaction using the silicon tetrachloride/stannic chloride method already described were also unsuccessful.

Fabrichnyi, Shalavina and Gold'farb (83) have reported the synthesis of thieno[b]cyclohexanone from 4-(thienyl-2)butyric acid by the method of cyclic dehydration using orthophosphoric acid in acetic anhydride. Attempts to utilise this method in this synthesis were unsuccessful. Attempts were made to effect a cyclic dehydration using polyphosphoric acid. In spite of using a wide variety of conditions, ranging from stirring a dilute solution of the acid in benzene at room temperature with PPA for periods ranging from ten minutes to several days, to heating the acid with PPA with no solvent, none of the required product was isolated.

In contrast to the difficulties experienced in preparing the parent thieno[b]tropone, the preparation of 2-methyl-4H-cyclohepta[3,2-b]thiophen-4-one (2-methylthieno[b]tropone) (CXXVI) was relatively straightforward. (Scheme 48). Acylation of 2-methylthiophen using glutaric anhydride and anhydrous aluminium chloride in nitrobenzene, as described by McGhie, Ross, Evans and Tomlin (84), followed by reduction of the carbonyl

group using the Huang-Minlon procedure (81) yielded the required pentanoic acid (CXVIII). Treatment of this with thionyl chloride in boiling anhydrous ether in the presence of a few drops of pyridine gave the corresponding acid chloride. Treatment of the crude acid chloride with anhydrous stannic chloride in carbon disulphide at room temperature, as described by Cagniant and Cagniant (82) led to the required 2-methylthieno[b]cycloheptanone (CXX). Bromination of this compound using bromine in carbon tetrachloride yielded 3,5,5-tribromo-2-methylthieno[b]cycloheptanone (CXXII). The isotope pattern in the mass spectrum of this compound indicated that three bromine atoms had been incorporated, and the disappearance from the n.m.r. spectrum of the cyclic ketone of the singlet at

3.1 p.p.m. due to the aromatic proton, and of the multiplet at 7.4-7.6 p.p.m. due to the protons adjacent to the carbonyl group confirmed the positions at which substitution had occurred.

Treatment of the tribromoketone with lithium chloride in boiling D.M.F. gave a 60% yield of 3-bromo-2-methylthieno[b]tropone (CXXIII). The spectral details of this compound were found to be very similar to those of benz[b]tropone, having infrared absorptions at 1630 and 1589 cm^{-1} (benz[b]tropone has i.r. maxima at 1640, 1609 and 1589 cm^{-1} (56)), similar ultra violet absorption showing the expected bathochromic shift on protonation by strong acid, and an n.m.r. spectrum in which all signals occur well downfield (fig. 1). As might be expected, the mass spectrum shows an initial loss of 28 (corresponding to loss of -CO-), followed by loss of 79 and 81 (Br) to give a base peak at m/e 147, which is presumably the molecular ion corresponding to benzthiophen.

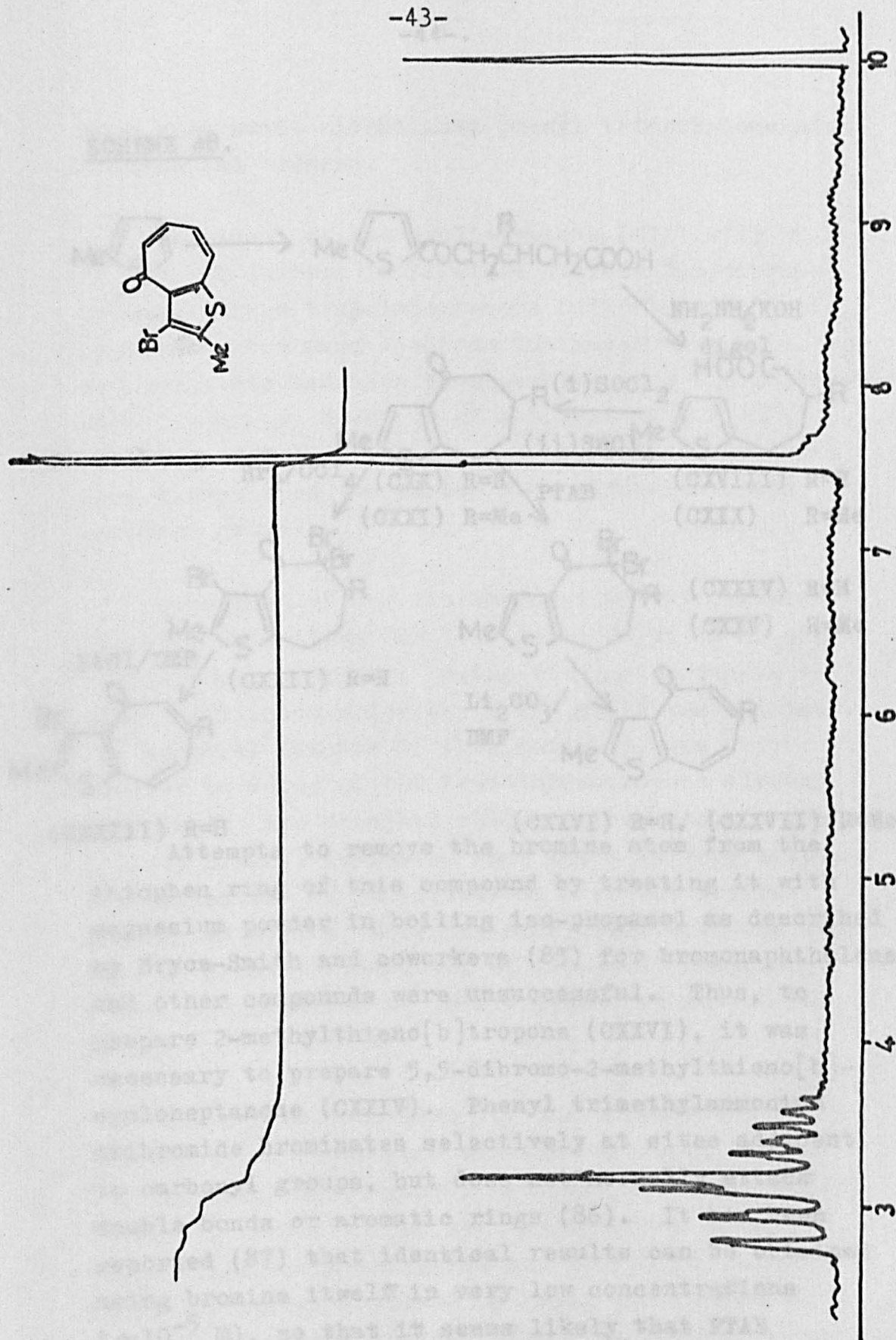
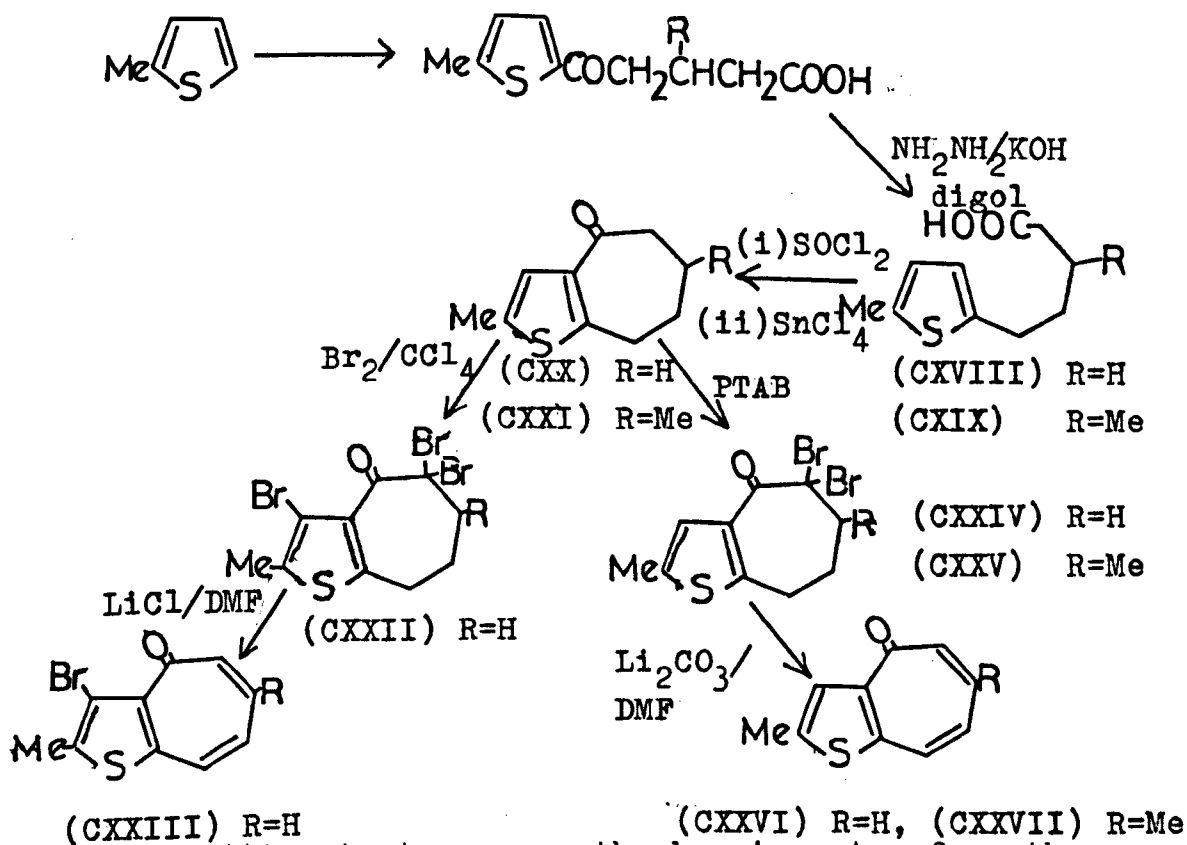


Fig. 1

SCHEME 48.



Attempts to remove the bromine atom from the thiophen ring of this compound by treating it with magnesium powder in boiling iso-propanol as described by Bryce-Smith and coworkers (85) for bromonaphthalene and other compounds were unsuccessful. Thus, to prepare 2-methylthieno[b]tropone (CXXVI), it was necessary to prepare 5,5-dibromo-2-methylthieno[b]-cycloheptanone (CXXIV). Phenyl trimethylammonium tribromide brominates selectively at sites adjacent to carbonyl groups, but does not normally attack double bonds or aromatic rings (86). It has been reported (87) that identical results can be obtained using bromine itself in very low concentrations ($\sim 10^{-5}$ M), so that it seems likely that PTAB functions in a similar way, presumably by dissociating

to a very small extent into phenyl trimethylammonium bromide and bromine.

Treatment of the cyclic ketone (CXX) with PTAB in dry THF at room temperature yielded 5,5-dibromo-2-methylthieno[b]cycloheptanone (CXXIV). The isotope pattern in the mass spectrum indicated that only two bromine atoms had been incorporated, and the absence from the n.m.r. spectrum of a signal at τ 7.4-7.6 p.p.m. and of a signal at τ 5.2 p.p.m. confirmed that both were situated on the carbon atom adjacent to the carbonyl group.

Treatment of the dibromocompound with lithium chloride in boiling DMF lead to a 60% yield of the thienotropone (CXXVI); using lithium carbonate in place of lithium chloride, a 77% yield was obtained. The spectral details of this compound were very similar to those of the bromothienotropone already described. The chemical shift of the aromatic proton (τ 2.5 p.p.m.) indicates that there is very little delocalisation of π -electrons over the entire conjugated system, which is consistent with the reported lack of aromatic character of troponoid compounds. The 60 MHz spectrum of this compound is shown in fig. 2.

The method described for the preparation of 2-methylthieno[b]tropone was also used, with minor modifications to prepare 2,6-dimethylthieno[b]tropone (CXXVII). Acylation of 2-methylthiophen using β -methylglutaric anhydride and aluminium chloride in nitrobenzene, followed by Huang-Minlon reduction and subsequent cyclisation gave 2,6-dimethylthieno[b]-

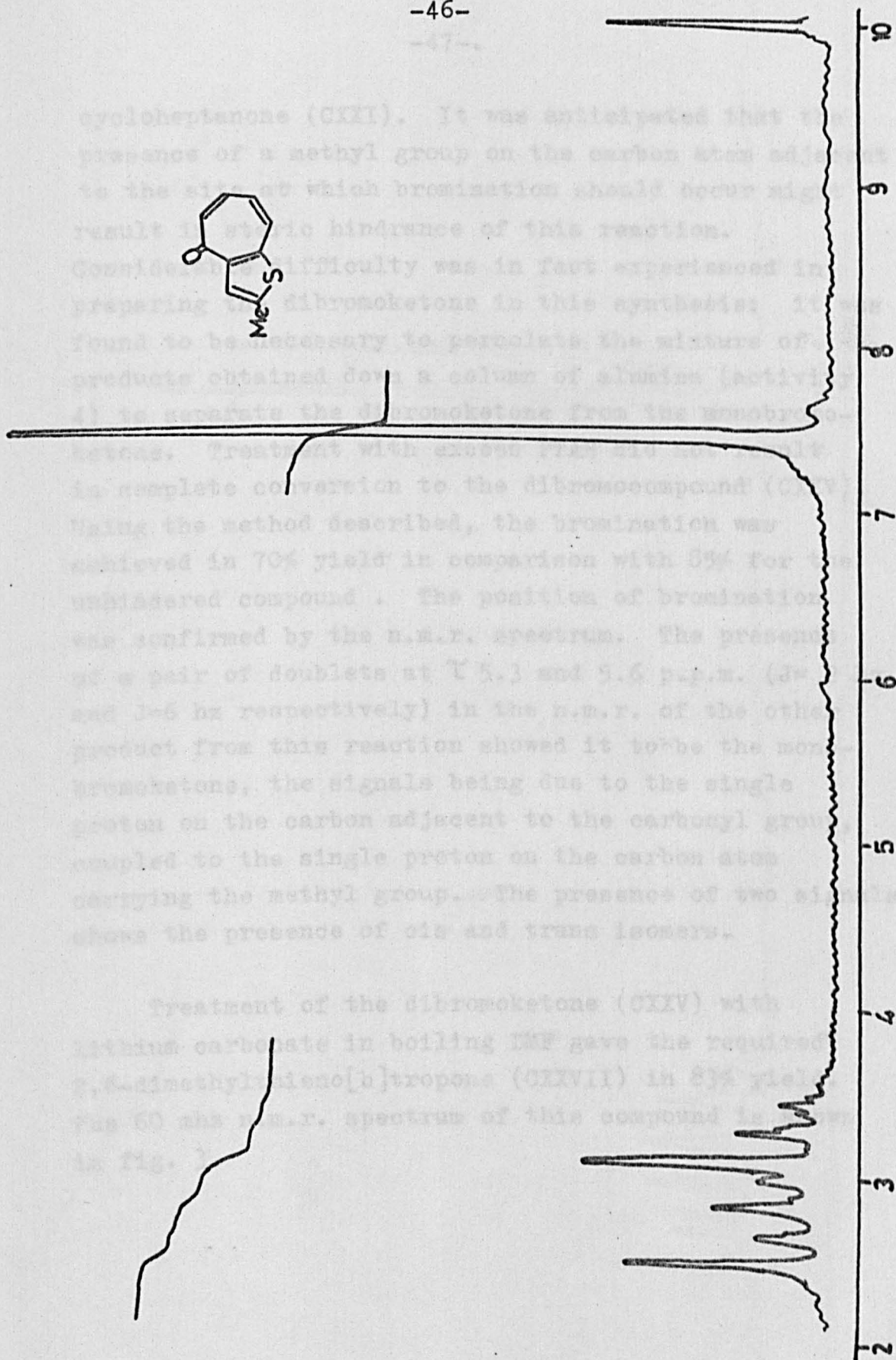
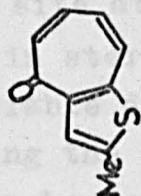


Fig. 2

cycloheptanone (CXXI). It was anticipated that the presence of a methyl group on the carbon atom adjacent to the site at which bromination should occur might result in steric hindrance of this reaction. Considerable difficulty was in fact experienced in preparing the dibromoketone in this synthesis; it was found to be necessary to percolate the mixture of products obtained down a column of alumina (activity 4) to separate the dibromoketone from the monobromoketone. Treatment with excess PTAB did not result in complete conversion to the dibromocompound (CXXV). Using the method described, the bromination was achieved in 70% yield in comparison with 85% for the unhindered compound. The position of bromination was confirmed by the n.m.r. spectrum. The presence of a pair of doublets at τ 5.3 and 5.6 p.p.m. ($J = 2$ hz and $J = 6$ hz respectively) in the n.m.r. of the other product from this reaction showed it to be the monobromoketone, the signals being due to the single proton on the carbon adjacent to the carbonyl group, coupled to the single proton on the carbon atom carrying the methyl group. The presence of two signals shows the presence of cis and trans isomers.

Treatment of the dibromoketone (CXXV) with lithium carbonate in boiling DMF gave the required 2,6-dimethylthieno[b]tropone (CXXVII) in 83% yield. The 60 mhz n.m.r. spectrum of this compound is shown in fig. 3.

For the synthesis of furan(2-yl)acetic acid (11), the general method of Birch and Birch (1951) was used. An intermediate furan(2-yl)acetic acid (11) was prepared by Birch and Birch (1951) and was used for the synthesis of furan(2-yl)acetic acid (11).

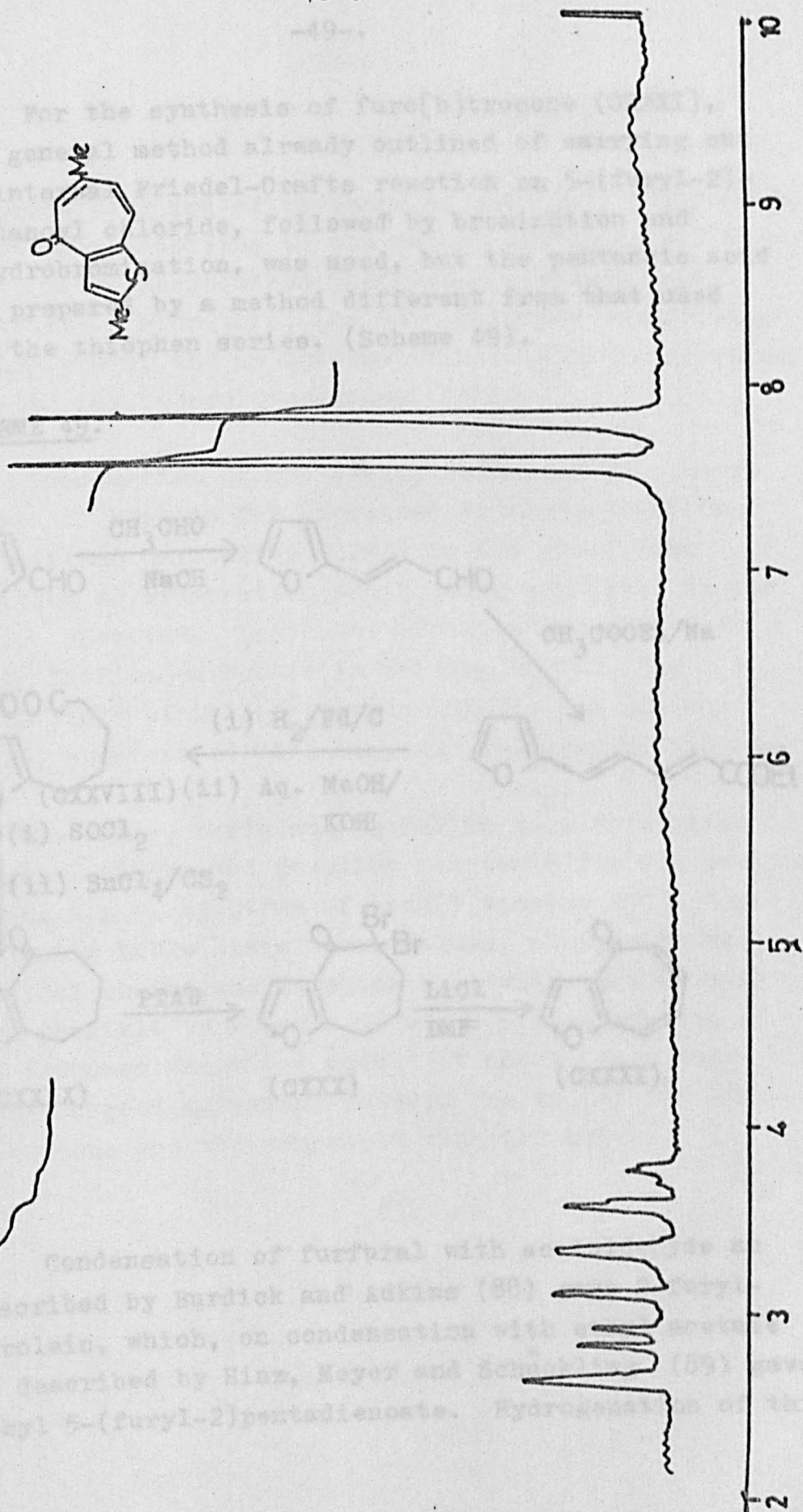
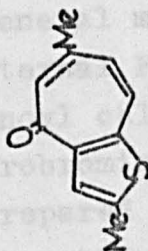
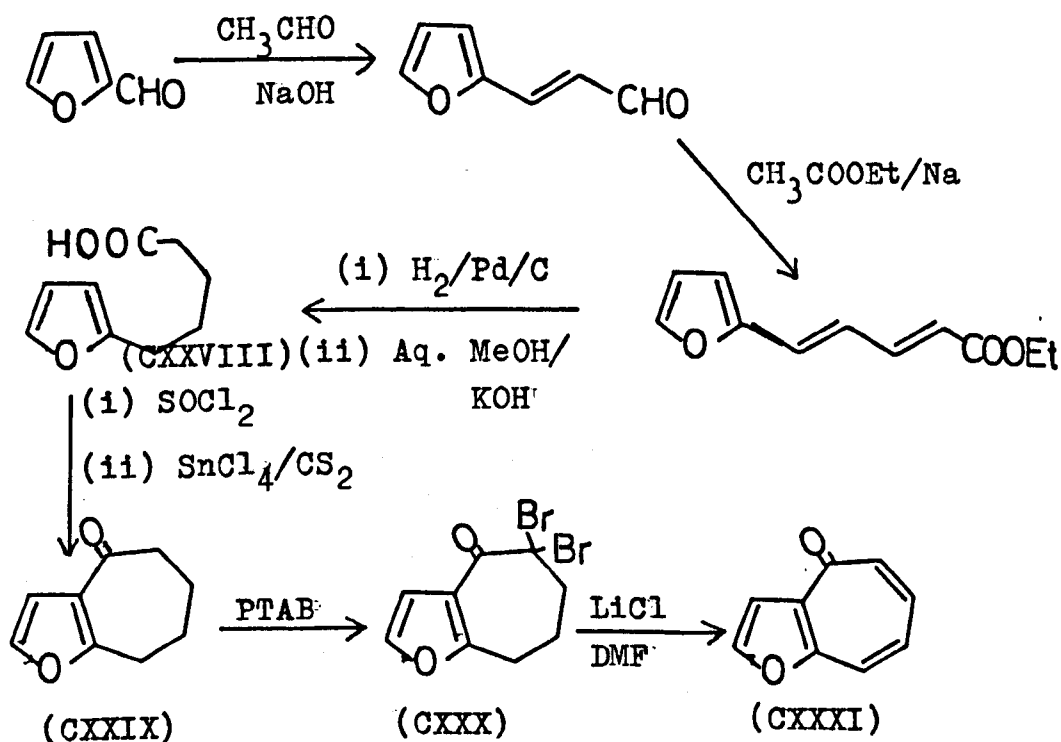


Fig. 3

For the synthesis of furo[b]tropone (CXXXI), the general method already outlined of carrying out an internal Friedel-Crafts reaction on 5-(furyl-2)-pentanoyl chloride, followed by bromination and dehydrobromination, was used, but the pentanoic acid was prepared by a method different from that used for the thiophen series. (Scheme 49).

SCHEME 49.



Condensation of furfural with acetaldehyde as described by Burdick and Adkins (88) gave 2-furylacrolein, which, on condensation with ethyl acetate as described by Hinz, Meyer and Schückling (89) gave ethyl 5-(furyl-2)pentadienoate. Hydrogenation of this

compound over palladium-charcoal catalyst, followed by hydrolysis according to the method of Treibs and Heyer (90), gave the required 5-(furyl-2)pentanoic acid (CXXVIII). From this, the acid chloride was prepared in 67% yield, and an internal Friedel-Crafts reaction led to furo[b]cycloheptanone (CXXIX).

Bromination of the cyclic ketone using a large excess of PTAB in THF proceeded slowly to give the 5,5-dibromo derivative (CXXX) in 60% yield, the position of bromination again being confirmed by the n.m.r. spectrum. Dehydrobromination was effected using lithium carbonate in boiling DMF to give a 52% yield of furo[b]tropone (CXXXI). A 220 mhz n.m.r. spectrum of this compound is shown in fig. 4.

Bertelli, Gerig and Herbellin have determined chemical shifts and coupling constants for all protons in the n.m.r. spectrum of benz[b]tropone (91). The following table lists these values, along with the chemical shifts and coupling constants that it has been possible to measure from the n.m.r. spectra of the tropones described here. It can be seen that there is good agreement between the values for benz[b]tropone and the compounds reported here.

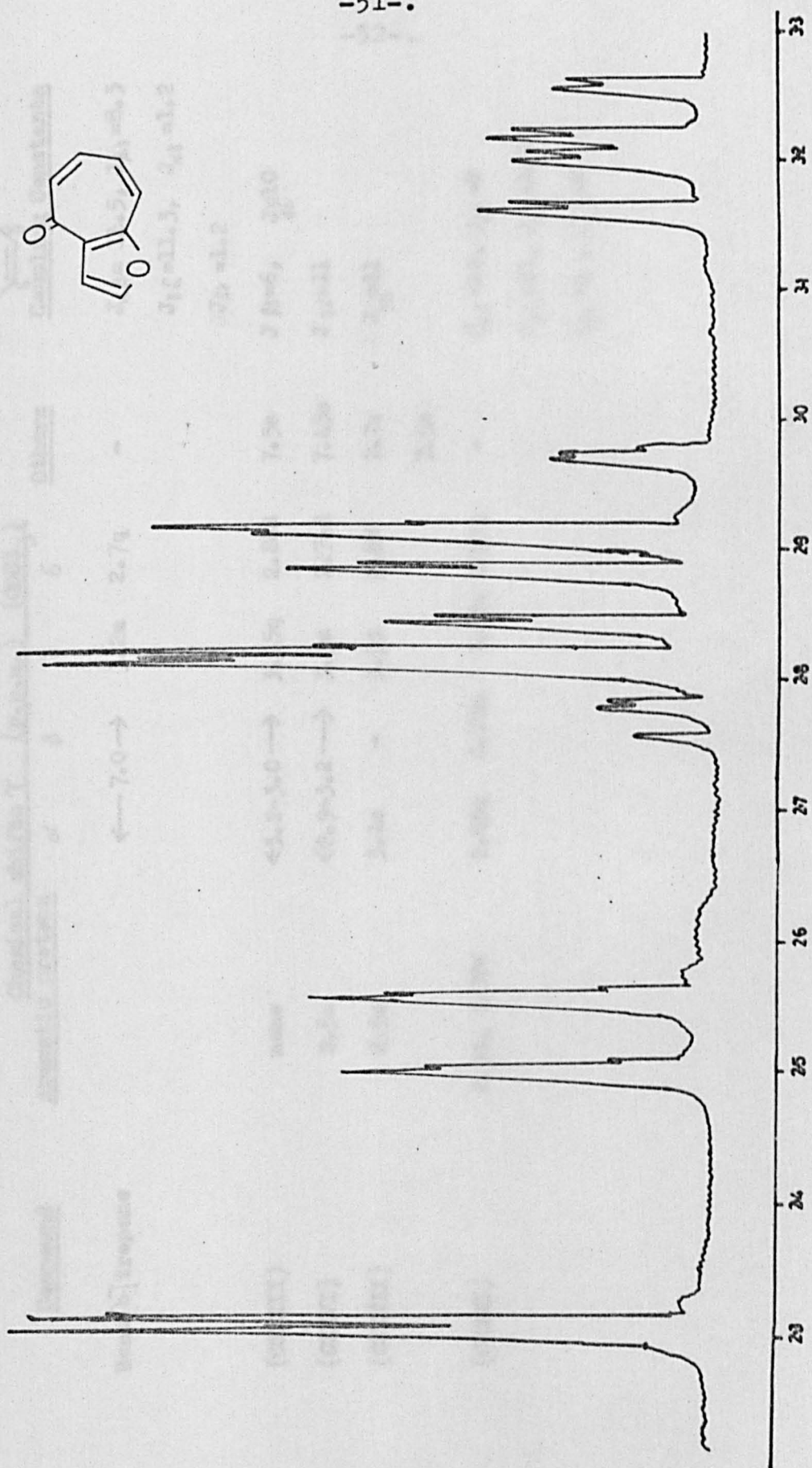



Fig. 4

Compound	N.m.r. data on terpenes						Others	 Coupling Constants
	Aromatic protons	Chemical shifts τ (p.p.m.) (CDCl ₃)						
		α	β	γ	δ			
Benz[b]terpene		$\leftarrow 7.0 \rightarrow$	3.2m	2.7q	-	-	$J_{\alpha\beta} = 11.5, J_{\beta\gamma} = 8.3$ $J_{\gamma\delta} = 11.3, J_{\alpha\delta} = 1.2$ $J_{\beta\delta} = 1.2$	
(CXXIII)	nene	$\leftarrow 3.2-3.0 \rightarrow$	3.45q	2.86d	7.5s	$J_{\beta\gamma} = 6, J_{\delta\delta} = 10$		
(CXXVI)	2.5s	$\leftarrow 2.9-3.2 \rightarrow$	3.3m	2.74d	7.45s	$J_{\gamma\delta} = 11$		
(CXXVII)	2.5s	3.1s	-	3.5d	2.8d	7.7s	$J_{\gamma\delta} = 11$	
						7.5s		
(CXXXI)	2.3d, 2.78d	2.85q	2.75m	3.15m	2.52q	-	$J_{\alpha\beta} = 12, J_{\beta\gamma} = 8$ $J_{\gamma\delta} = 11, J_{\alpha\delta} = 1.5$ $J_{\beta\delta} = 1, J_{2,3} = 2$	

EXPERIMENTAL

Preliminary Notes

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

Infrared absorption spectra were measured on a Perkin-Elmer 257 spectrophotometer, either in solution (e.g. CHCl_3), or as Nujol mulls (mull).

Electronic absorption spectra were recorded on a Unicam SP 800 instrument; the figures in brackets following the position of absorption maxima are $\log_{10} \epsilon$.

Nuclear magnetic resonance spectra are measured either at 60 MHz on a Perkin Elmer R10 instrument, or at 220 MHz on a Varian instrument. The chemical shifts are quoted as 'tau' (τ) values from an internal tetramethylsilane standard (10.0 τ), and coupling constants are quoted in Hz. The following abbreviations are used: s=singlet, d=doublet, tr=triplet, q=quartet, m=multiplet.

Microanalyses were carried out on an F. & M. carbon/hydrogen/nitrogen analyser at the University of Keele.

Mass spectra were determined on an Hitachi-Perkin Elmer RMU 6 instrument.

Preparative layer chromatography (p.l.c.) was carried out on 40 x 20 cm. glass plates coated with a 1.5 mm. layer of Kieselgel PF₂₅₄. The separated components, visualised under ultraviolet light, were isolated by scraping off the silica and extracting several times with hot methanol. The filtered methanolic solution was evaporated to leave a residue which contained some silica. This residue was then dissolved in chloroform, filtered, dried and evaporated.

40-60 petrol refers to petroleum ether having a boiling point range 40-60°.

Unless otherwise stated, the melting points/boiling points of known compounds are taken from the same source as the experimental details.

4-(Thenoyl-2)butanoic acid

Monomethyl glutarate (87.5 g) and silicon tetrachloride (25.5 g) were dissolved in 700 ml of benzene, and the solution was boiled under reflux until the evolution of HCl ceased. The mixture was then cooled to 0°C and anhydrous stannic chloride (65 g) in dry benzene (150 ml) was added dropwise. The mixture was then boiled under reflux for two hours, cooled and poured onto ice. The crude ester was extracted with chloroform, the solution dried (sodium sulphate) and the solvent removed. The product was purified by distillation under reduced pressure, b.p. 128°/0.1mm (lit. (79) 186-7°/15mm), (53 g, 50%).

N.m.r. τ	2.2-2.4	2H (m)	H on C5 and C3 of ring
(CDCl ₃)	2.8-3.0	1H (m)	H on C4 of ring
	6.3	3H (s)	-OMe
	7.0	2H (tr, J=6)	-CH ₂ adjacent to carbonyl group
	7.6-8.1 p.p.m.	4H (m)	remaining -CH ₂ - groups

The ester was hydrolysed to the acid by boiling under reflux with 10% methanolic sodium hydroxide solution. The mixture was then poured onto ice and the unreacted ester was extracted with chloroform. The solution was then made acidic with hydrochloric acid, cooled in an ice bath and the acid removed by filtration. Recrystallisation from benzene/40-60 petrol gave 4-(thenoyl-2)butanoic acid as a white crystalline solid, m.p. 91° (lit.(79) 91°) (85%).

N.m.r. τ -1.6	p.p.m. 1H (s) -COOH
(CDCl ₃) 1.9-2.2	2H (m) H on C5 and C3
2.5-2.7	1H (m) H on C4
6.9	2H (tr, J=6) -CH ₂ - adjacent to carbonyl group
7.4	2H (tr, J=6) -CH ₂ - adjacent to carboxyl group
7.6-7.8	2H (m) remaining -CH ₂ -

5-(Thienyl-2)pentanoic acid

Prepared using the method described by Badger, Rodda and Sasse (8B) for a similar compound. B.p. 148-50°/1 mm, m.p. 36° (lit. b.p. 178°/14mm, m.p. 36°) (60%).

N.m.r. τ -0.8	p.p.m. 1H (s) -COOH
(CCl ₄) 3.0	1H (q, J _{4,5} =5, J _{3,5} =2) H on C5
3.1-3.4	2H (m) H on C3 and C4
7.1-7.4	2H (m) -CH ₂ - adjacent to ring
7.6-7.9	2H (m) -CH ₂ - adjacent to carboxyl group
8.2-8.5	4H (m) remaining -CH ₂ -

4-(5-Methylthenoyl-2)butyric acid

Prepared in 70% yield according to the method of McGhie, Ross, Evans and Tomlin (84). M.p. 119° (lit. 118-20°).

N.m.r. τ -0.8	p.p.m. 1H (s) -COOH
2.4	1H (d, J=4) H on C3 of ring
3.2	1H (d, J=4) H on C4 of ring
7.1	4H (tr, J=6) -CH ₂ - adjacent to ring and carboxyl group
7.6	3H (s) methyl group
7.7-8.1	4H (m) remaining -CH ₂ - groups

5-(5-Methylthienyl-2)pentanoic acid (CXVIII)

Prepared in 60% yield according to the method described by Badger, Rodda and Sasse (81) for a similar compound. B.p. 160-2°/0.5 mm, (m.p. 57° (lit. (82)) b.p. 200°/17 mm, m.p. 57.5°).

N.m.r. τ	-1.5	p.p.m.	1H (s) -COOH
(CCl ₄)	3.3		2H (s) ring proton
	7.15		2H (m) -CH ₂ - adjacent to ring
	7.50		3H (s) methyl group
	7.55		2H (m) -CH ₂ - adjacent to carboxyl group
	8.0-8.4		4H (m) remaining -CH ₂ - groups

5,6,7,8-Tetrahydro-2-methyl-4H-cyclohepta[3,2-b]thiopen-4-one. (CXX).

Prepared in 60% yield according to the method of P. Cagniant and D. Cagniant (82). B.p. 108°/1.3 mm (lit. 157°/7 mm).

N.m.r. τ	3.1	p.p.m.	1H (s) aromatic proton
(CCl ₄)	7.0-7.2		2H (m) -CH ₂ - adjacent to ring
	7.4-7.6		2H (m) -CH ₂ - adjacent to carbonyl group
	7.7		3H (s) methyl group
	8.1-8.3		4H (m) remaining -CH ₂ - groups

3,5,5-Tribromo-5,6,7,8-tetrahydro-2-methyl-4H-cyclohepta[3,2-b]thiophen-4-one (CXXII).

A solution of bromine (6.5 ml) in carbon tetrachloride (30 ml) was added dropwise to a stirred

solution of the cyclic ketone (CXX) in carbon tetrachloride (50 ml) containing potassium carbonate (17.4 g). The mixture was stirred overnight, filtered, the solid washed with chloroform, and the total organic solutions evaporated. The tribromoketone was recrystallised from methanol. M.p. 132°. (16.5 g 95%).

Analysis: $C_{10}H_9OSBr_3$ requires C=28.8% H=2.20%
found C=29.1% H=2.09%

I.r. (mull) 1560 cm^{-1} (-CO-)

U.v. (EtOH) 232 nm (sh) 268 nm (3.32)

N.m.r. τ 6.9-7.1 p.p.m. 4H (m) protons on C6 and C8

($CDCl_3$) 7.6 3H (s) methyl group

7.8-8.0 2H (m) protons on C7

M.s. 420, 418, 416, 414 (M^+) (1:3:3:1)

3-Bromo-2-methyl-4H-cyclohepta[3,2-b]thiophen-4-one
(CXXIII)

A mixture of the tribromoketone (CXXII) (5 g) and lithium chloride (1.52 g) in N,N-dimethylformamide (50 ml) was boiled under nitrogen for 2 h. Removal of the solvent under reduced pressure, followed by dilution of the residue with water gave a product which was extracted with chloroform. The dried solution was evaporated, and the residue crystallised from methanol to give the bromotropone as pale yellow needles, m.p. 144-5° (1.85 g, 60%).

Analysis: $C_{10}H_7OSBr$ requires C=47.1% H=2.79%
found C=47.0% H=2.88%

I.r. (CHCl_3) 1630, 1590 cm^{-1}
 U.v. (EtOH) 245 (4.29), 268 (sh), 335 nm (3.95)
 (H_2SO_4) 225 (4.10), 253 (4.43), 283 (4.34),
 356 (4.76), 421 nm (4.63)
 N.m.r. τ 2.86 p.p.m. 1H (d, $J_{7,8}=10$) H on C8
 (CDCl_3) 3.0-3.2 2H (m) H on C5 and C6
 3.45 1H (q, $J_{7,8}=10$, $J_{6,7}=6$)
 H on C7
 7.5 3H (s) methyl group
 M.s. 256, 254 (M^+) (1:1)

5,5-Dibromo-5,6,7,8-tetrahydro-2-methyl-4H-cyclo-
 hepta[3,2-b]thiophen-4-one (CXXIV)

Phenyltrimethylammonium tribromide (4.2 g) was added to a stirred solution of the cyclic ketone (CXX) (1 g) in dry tetrahydrofuran (THF) (30 ml). The mixture was stirred for 24 h at room temperature and then filtered. The solid was washed with THF and the combined solutions were evaporated. The product was obtained as colourless crystals from methanol, m.p. 79-80° (1.6 g, 85%).

Analysis: $\text{C}_{10}\text{H}_{10}\text{OSBr}_2$ requires C=35.5% H=2.99%
 found C=35.9%, H=2.89%

I.r. (mull) 1555 cm^{-1} (-CO-)
 U.v. (EtOH) 230 (sh), 266 nm (3.38)
 N.m.r. τ 3.0 p.p.m. 1H (s) aromatic proton
 (CDCl_3) 6.6-7.0 4H (m) $-\text{CH}_2-$ groups adjacent to
 aromatic ring and $-\text{CBr}_2-$
 7.7 3H (s) methyl group
 7.8-8.0 2H (m) remaining $-\text{CH}_2-$ group
 M.s. 340, 338, 336 (M^+), (1:2:1)

2-Methyl-4H-cyclohepta[3,2-b]thiophen-4-one (CXXVI)

A mixture of the dibromoketone (CXXIV) (5g) and lithium carbonate (3.5 g) in anhydrous DMF was boiled under reflux for 2.5 h in an atmosphere of nitrogen. The mixture was worked up as described for compound (CXXIII) to give the methylthienotropone as pale yellow needles from cyclohexane, m.p. 64-5° (2 g, 77%).

Analysis: $C_{10}H_8OS$ requires C=68.2% H=4.55%
found C=68.0% H=4.63%

I.r. (CCl_4) 1630, 1590 cm^{-1}

U.v. (EtOH) 242 (4.27), 330 (3.93), 350 (3.90),
365 nm (3.88)

(H_2SO_4) 247 (4.02), 275 (4.03), 293 (sh),
325 (3.33), 335 (3.38), 405 nm (3.47)

N.m.r. τ 2.5 p.p.m.. 1H (s) H on C3
($CDCl_3$) 2.74 1H (d, J=11) H on C8
2.9-3.2 2H (m) H on C5 and C6
3.3 1H (m) H on C7
7.45 3H (s) methyl group

M.s. 176 (M^+)

3-Methyl-4-(5-methylthenoyl-2)butyric acid

To a vigorously stirred solution of 2-methylthiophen (27.5 g) and β -methylglutaric anhydride (30 g) in nitrobenzene (250 ml) at 0° was added aluminium chloride (74 g) over 1 h. The mixture was then stirred 1 h at room temperature and hydrolysed using a mixture of hydrochloric acid and ice. Following the removal of the nitrobenzene by steam distillation, the crude product was isolated by filtration. Recrystallisation from benzene/40-60 petrol gave the keto-acid, m.p. 79-80° (36 g, 70%). (Note: working on a scale 10% of that reported above, the yield of keto-acid was 93%).

Analysis: $C_{11}H_{14}O_3S$ requires C=58.4%, H=6.23%
found C=57.9%, H=6.16%

I.r. ($CHCl_3$) 1710 ($-COOH$), 1650 cm^{-1} ($=CO-$)
U.v. (EtOH) 264 (3.90), 296 nm (3.99)

N.m.r. τ -0.8 p.p.m. 1H (s) $-COOH$
($CDCl_3$) 2.4 1H (d, J=5) H on C3 of ring
3.2 1H (d, J=5) H on C4 of ring
7.2 2H (m) $-CH_2-$ adjacent to
carbonyl group
7.5 3H (s) methyl group on ring
7.6 3H (m) $-CHMe-$ and $-CH_2-$
adjacent to carboxyl
8.9 3H (d, J=5) methyl group

3-Methyl-5-(5-methylthienyl-2)pentanoic acid (CXIX)

A solution of 3-methyl-4-(5-methylthienoyl-2)-butyric acid (16.3 g) and 100% hydrazine hydrate (9.2 ml) in di-ethylene glycol^o (100 ml) and water (5 ml) was heated with distillation to 180°. The mixture was then cooled to 100°, potassium hydroxide (14 g) was added, and the mixture boiled under reflux for a further 4 h. The cooled mixture was poured into water, washed with ether, the aqueous layer acidified and the product extracted with ether. The solution was dried (Na_2SO_4), the solvent removed and the residue distilled under reduced pressure to give the methyl-pentanoic acid, b.p. 150-2°/1mm, m.p. 43-3° (40-60 petrol), (6.4 g, 42%).

Analysis: $C_{11}H_{16}O_2S$ requires C=62.2%, H=7.59%
found C=62.0%, H=7.67%

I.r. ($CHCl_3$) 1710 cm^{-1} ($-COOH$)

U.v. (EtOH)	233 nm (2.87)	
N.m.r. τ	-0.7	p.p.m. 1H (s) -COOH
(CDCl ₃)	3.4	2H (s) ring protons
	7.2	2H (tr, J=6) -CH ₂ - adjacent to ring
	7.6	3H (s) methyl group on ring
	7.8-8.0	3H (m) -CHMe- and -CH ₂ - adjacent to carboxyl group
	8.1-8.4	2H (m) remaining -CH ₂ -
	8.9	3H (d, J=5) methyl group

5,6,7,8-Tetrahydro-2,6-dimethyl-4H-cyclohepta[3,2-b]-thiophen-4-one (CXXI).

Purified thionyl chloride (18 ml) was added to a solution of the pentanoic acid (CXIX) (24 g) in absolute ether (100 ml) containing several drops of pyridine. The mixture was boiled under reflux for 5 h, after which the excess thionyl chloride and solvent were removed under reduced pressure. The crude acid chloride was dissolved in dry carbon disulphide (500 ml) and cooled to 0°. Stannic chloride (25 ml) was added with stirring, after which the mixture was stirred at room temperature for 2.5 h. Ice and hydrochloric acid were added, the organic layer was separated and dried (Na₂SO₄), and distillation under nitrogen gave the cyclic ketone as a colourless liquid, b.p. 121-4°/1.5 mm, which solidified on standing.

Analysis: C₁₁H₁₄OS requires C=68.0%, H=7.26%
found C=68.1% H=7.30%

I.r. (CCl ₄)	1670 cm ⁻¹	(-CO-)
U.v. (EtOH)	226 (4.12), 256 (4.08), 283 nm	(sh)
N.m.r. τ	2.8	p.p.m. 1H (s) thiophen proton
(CCl ₄)	7.0	2H (tr, J=6) -CH ₂ - adjacent to aromatic ring
	7.3-7.5	2H (m) -CH ₂ - adjacent to carbonyl group

7.6	3H (s) methyl group on aromatic ring
7.7-8.2	3H (m) -CHMe- and -CH ₂ -
8.9	3H (d, J=5) methyl group

5,5-Dibromo-5,6,7,8-tetrahydro-2,6-dimethyl-4H-cyclohepta[3,2-b]thiophen-4-one (CXXV)

To a solution of the cyclic ketone (CXXI) (1 g) in dry THF (30 ml) was added PTAB (4 g). The mixture was stirred at room temperature (4 h), filtered, and the white solid washed with THF. The combined organic solutions were evaporated under reduced pressure. The resulting oil was dissolved in a small volume of chloroform and percolated down a column of alumina (activity 4) with 40-60 petrol, to give the required dibromoketone as colourless platelets from methanol, m.p. 69-70° (1.3 g, 70%).

Analysis $C_{11}H_{12}OSBr_2$ requires C=37.5%, H=3.44%
found: C=37.7%, H=3.90%

I.r. (CHCl₃) 1670 cm⁻¹ (-CO-)

U.v. (EtOH) 229 (sh), 265 (2.84), 305 nm (sh)

N.m.r. τ 3.05 p.p.m. 1H (s) thiophen proton
6.8-7.2 3H (m) -CHMe- and -CH₂- adjacent to aromatic ring

7.6 3H (s) methyl group on thiophen ring

7.8-8.3 2H (m) remaining -CH₂-

8.6 3H (d, J=6) methyl group

M.s. 354, 352, 350 (M⁺)

2,6-Dimethyl-4H-cyclohepta[3,2-b]thiophen-4-one (CXXVII)

A solution of the dibromoketone (CXXV) (1 g) and lithium carbonate (0.5 g) in anhydrous DMF (50 ml)

were boiled under reflux in an atmosphere of nitrogen for 2½ h and worked up as described for compound (CXXIII) to yield the tropone (CXXVII) as pale yellow needles from 60-80 petrol, m.p. 132-3° (0.45 g, 83%).

I.r. (CHCl ₃)	1620, 1560 cm ⁻¹
U.v. (EtOH)	245 (4.87), 332 (4.38), 344 (sh) 360 nm (4.31)
(H ₂ SO ₄)	248 (4.03), 280 (4.12) 322 (4.22) 340 (3.21), 398 nm (3.42)
N.m.r. τ	2.5 p.p.m. 1H (s) thiophen proton
(CDCl ₃)	2.8 1H (d, J _{7,8} =11) H on C8
	3.1 1H (s) H on C5
	3.5 1H (d, J _{7,8} =11) H on C7
	7.5 3H (s) methyl group on thiophen ring
	7.7 3H (s) methyl group on tropone ring
M.s.	190.0446 (M ⁺) (C ₁₁ H ₁₀ OS requires 190.0453)

2-Furylacrolein

Prepared as described by Burdick and Adkins (88) in 42% yield, b.p. 128-32°/18 mm, m.p. 53° (lit. (92) b.p. 110-15°/15 mm, m.p. 53°).

N.m.r. τ	0.4 p.p.m. 1H (d, J=8) -CHO
(CDCl ₃)	2.4 1H (d, J=2), H on C5 of ring
	2.8 1H (d, J=18) -CH= adjacent to ring
	3.3 1H (q, J _{3,4} =5, J _{4,5} =2) H on C4 of ring
	3.4-3.6 2H (m) -CH= adjacent to -CHO and H on C3 of ring.

Ethyl 5-(furyl-2)pentadienoate.

Prepared in 70% yield according to the method of Hinz, Meyer and Schückling. (89). B.p. 118-20°/1mm (lit. 145-50°/10mm), solidifying on standing.

5-(Furyl-2)pentanoic acid (CXXVIII)

Prepared in 75% yield from ethyl 5-(furyl-2)-pentadienoate via ethyl 5-(furyl-2)pentanoate, as described by Treibs and Heyer (90). B.p. 115-16°/1mm, (lit. 122-5°/2 mm).

N.m.r. (ester) τ 2.8	p.p.m. 1H (d, J=2) H on C5 of furan ring
	3.8-3.9 1H (m) H on C4 of ring
	4.1-4.2 1H (m) H on C3 of ring
	6.0 2H (q, J=7) -OCH ₂ -
	7.2-7.5 2H (m) -CH ₂ - adjacent to furan ring
	7.7-7.9 2H (m) -CH ₂ - adjacent to -COOEt group
	8.2-8.4 4H (m) remaining -CH ₂ -
	8.8 3H (tr, J=7) -OCH ₂ CH ₃
(CCl ₄) (acid) τ -0.4	p.p.m. 1H (s) -COOH
	2.8 1H (d, J=2) H on C5 of furan ring
	3.8-3.9 1H (m) H on C4 of ring
	4.1-4.2 1H (m) H on C3 of ring
	7.3-7.6 2H (m) -CH ₂ - adjacent to furan ring
	7.6-7.8 2H (m) -CH ₂ - adjacent to -COOH group
	8.1-8.5 4H (m) remaining -CH ₂ -

5-(Furyl-2)pentanoyl chloride

Prepared in 67% yield according to the method of Treibs and Heyer (90), b.p. 120-5°/17 mm (lit. 95°/3mm).

5,6,7,8-Tetrahydro-4H-cyclohepta[3,2-b]furan-4-one.
(CXXIX)

Prepared in 33% yield as described by Treibs and
Hoyer (90), b.p. 130-1°/17mm (lit. 83-5°/2mm).

N.m.r.	τ	2.7	p.p.m.	1H (m)	H on C2
(CDCl ₃)		3.2		1H (m)	H on C3
		6.9-7.2		2H (m)	-CH ₂ - adjacent to aromatic ring
		7.2-7.5		2H (m)	-CH ₂ - adjacent to carbonyl groups
		8.0-8.3		4H (m)	remaining -CH ₂ - groups

5,5-Dibromo-5,6,7,8-tetrahydro-4H-cyclohepta[3,2-b]-furan-4-one (CXXX)

The bicycloheptafulranone (CXXIX) was dissolved in dry THF and excess PTAB was added. The mixture was stirred at room temperature for 5 h. Decomposition of the excess PTAB with acetone, followed by filtration and evaporation of the filtrate gave a gum which, on trituration with methanol gave the dibromoketone as colourless plates, m.p. 113-4° (from methanol) (60%).

Analysis	$C_9H_8O_2Br_2$	requires	C=35.1%	H=2.60%
		found	C=35.0%	H=2.45%

I.r. (CCl_4) 1670 cm^{-1} ($-\text{CO}-$)

U.v. (EtOH) 228 (sh), 290 nm (3.72)
 N.m.r. τ 2.7 p.p.m. 1H (d, J=2) H on C2
 (CDCl₃) 3.2 1H (d, J=2) H on C3
 6.9 4H (tr, J=5) H on C6 and C8
 7.6-8.0 2H (m) H on C7
 M.s. 310, 308, 306 (M⁺) (1:2:1)

4H-Cyclohepta[3,2-b]furan-4-one (CXXXI)

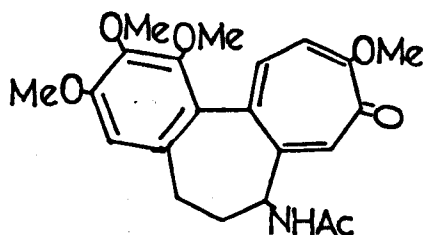
The dibromoketone (CXXX) (3 g) and lithium carbonate (1.5 g) in anhydrous DMF (50 ml) were boiled under reflux in an atmosphere for 3 h. Working up in the usual way gave 0.78 g (52%) of the crude furotropone, b.p. 110°/0.5 mm. Purification by p.l.c. (CHCl₃/benzene, 1:1, two elutions), followed by bulb-tube distillation gave an analytical sample having m.p. 39-41°.

Analysis C₉H₆O₂ requires C=74.0%, H=4.15%
 found C=73.7%, H=4.10%
 I.r. (CCl₄) 1630 and 1590 cm⁻¹
 U.v. (EtOH) 244 (sh), 259 (sh) 270 (sh) 300 (3.72)
 311 (3.79), 341 (3.83), 355 (3.80),
 372 nm (sh)
 N.m.r. τ 2.30 p.p.m. 1H (d, J_{2,3}=2) H on C2
 (CDCl₃) 2.52 1H (q, J_{7,8}=11, J_{6,8}=1)
 H on C8
 2.75 1H (m) H on C6
 2.78 1H (d, J_{2,3}=2) H on C3
 2.85 1H (q, J_{5,6}=12, J_{5,7}=1.5)
 H on C5
 3.15 1H (m) H on C7

PART 2

REVIEW

The first recorded photochemical reaction of a troponoid compound was published in 1865 when Hübler (93) reported that solutions of colchicine (CXXXII) turned brown on standing in sunlight. It was however ninety years before much progress was made in elucidating the structures of the photoproducts formed in this reaction; it was necessary to consider first the photochemistry of much simpler troponoid compounds in order to learn what sort of transformation was possible.



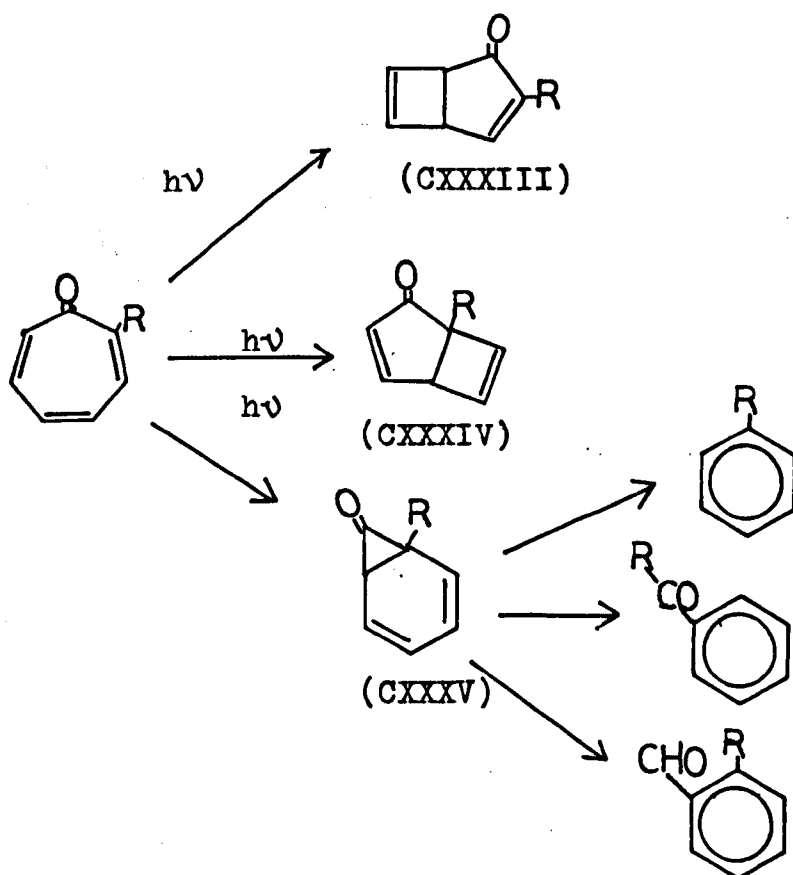
(CXXXII)

In 1960, Chapman and Pasto (94) published an account of the photochemical rearrangements of

γ -tropolone methyl ether. They prefaced their account with a discussion of the possible photoreactions of troponoid compounds, proposing three possible pathways governed by the nature of any substituents on the tropane ring, and also by any constraints due to fusion with other rings. (Scheme 50). They envisaged a valence tautomerisation to either of the bicyclo[3.2.0.] ring systems (CXXXIII) and (CXXXIV),

or to a norcaradienone structure (CXXXV), which could then undergo any of the three subsequent reactions shown to yield a variety of benzenoid compounds.

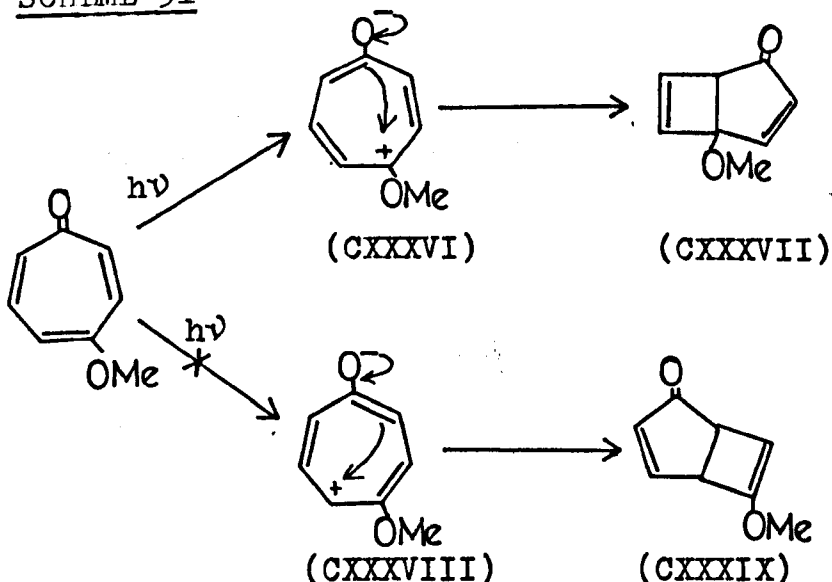
SCHEME 50.



γ -Tropolone methyl ether was reported to yield only one product of the type described, (CXXXVII), plus a quantity of polymeric material. The mechanism proposed could in principle lead to either of the two bicyclic systems shown (CXXXVII) and (CXXXIX), but it was felt that the intermediate (CXXXVI) would be stabilised by having the positive charge on the carbon atom carrying the methoxyl group, whereas the

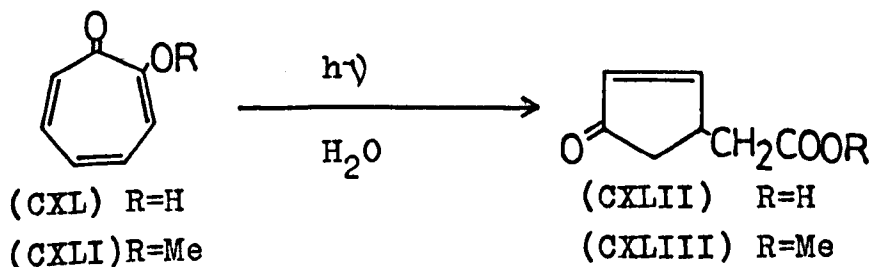
intermediate (CXXXVIII) would not, and that this difference accounted for the formation of only one bicyclic system in this case. (Scheme 51).

SCHEME 51



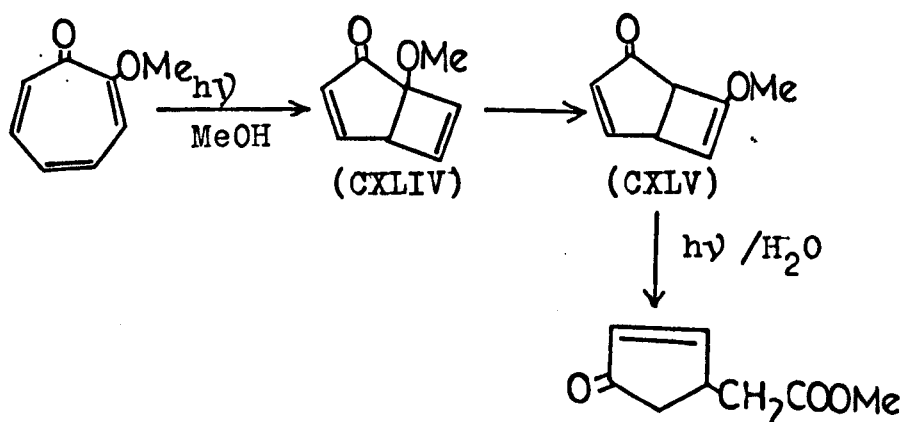
In 1959, Dauben, Koch and Thiessen (95) reported the photolysis of α -tropolone (CXL) in water to yield 4-oxo-2-cyclopentene-1-acetic acid (CXLII), and proposed a mechanism for this transformation, which was shown to be invalid when, in the following year, Forbes and Ripley (96) reported the photolysis of α -tropolone methyl ether (CXLI) in aqueous solution to give the methyl ester of 4-oxo-2-cyclopentene-1-acetic acid. (CXLIII). (Scheme 52).

SCHEME 52



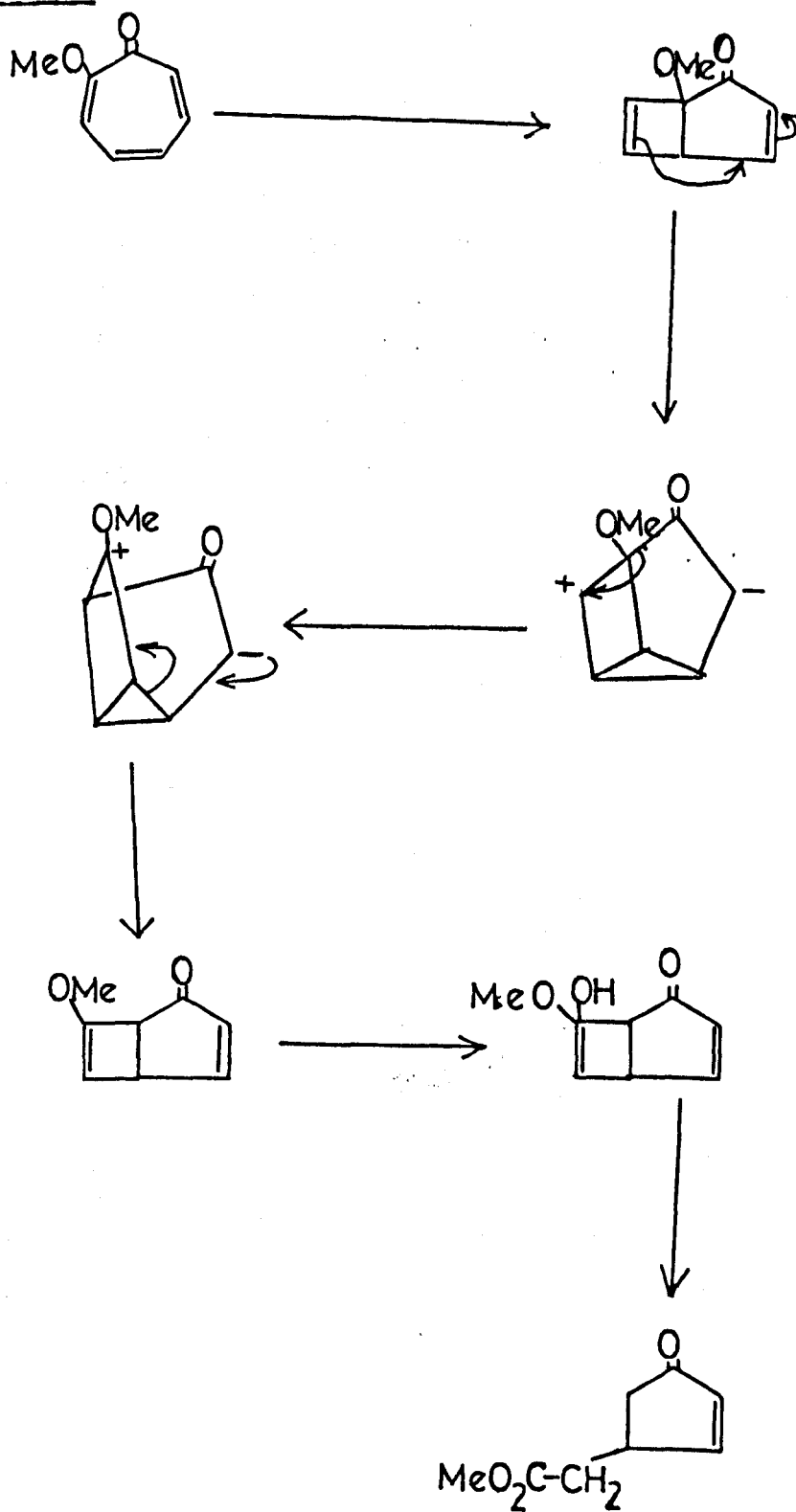
Dauben and coworkers (97) subsequently reported that irradiation of α -tropolone methyl ether in methanol gave rise initially to a bicyclic system (CXLIV) of the type predicted by Chapman and Pasto, which underwent rearrangement to another bicyclic system (CXLV). Addition of water followed by further irradiation lead to formation of the methyl ester as previously reported by Forbes and Ripley. The reaction was followed by G.L.C. and the products separated by preparative G.L.C. (Scheme 53).

SCHEME 53

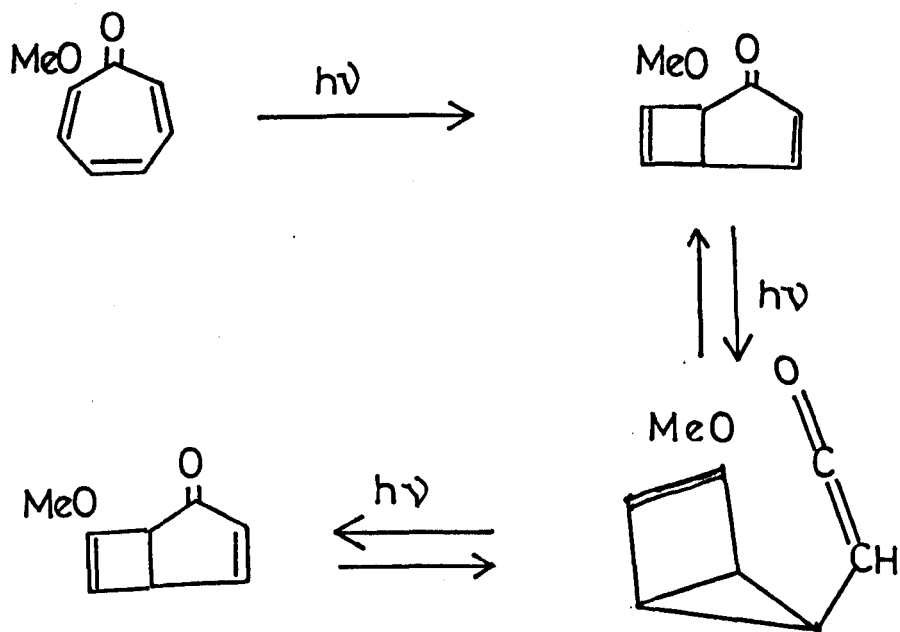


The mechanism for this sequence of reactions was determined by studying the photolysis of 4-methyltropolone methyl ether and 6-methyltropolone methyl ether; the mechanism was verified by its correct prediction of the photoproducts of thujaplicin methyl ether. The mechanism is shown in Scheme 54.

SCHEME 54



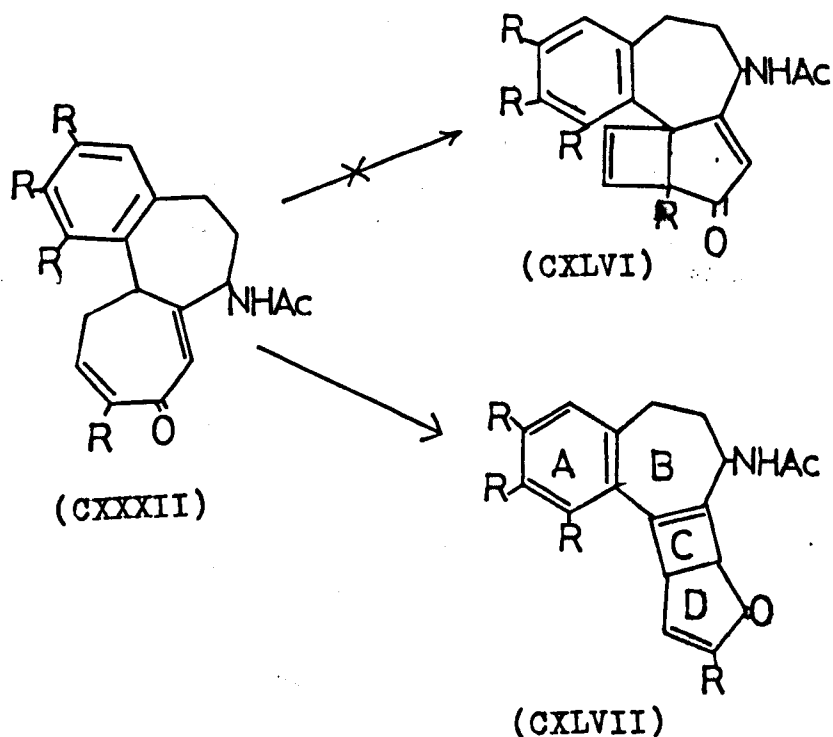
Further investigations of this photolysis by Chapman and Lassila (110) have shown it to proceed via a ketene intermediate. The presence of such an intermediate was indicated by the appearance of a band in the i.r. spectrum of the reaction mixture at 2118 cm^{-1} , which appeared after two minutes' irradiation and reached a maximum after 1-3 h. This band was observable only when the photolysis was carried out at temperatures below -70°C .



Neither β -tropolone methyl ether nor tropone itself undergo the photoisomerisations described above. It has been found however that some of the more complex troponoid compounds undergo these types of change.

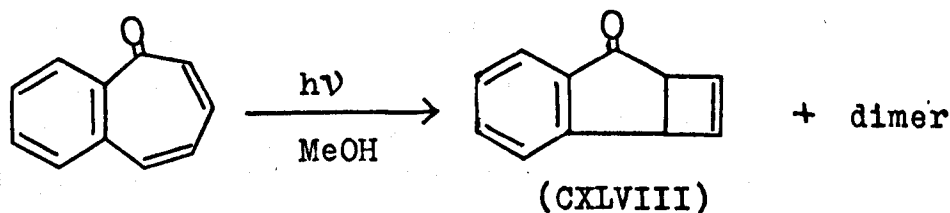
Work by Forbes (98) and Gardner and coworkers (99) showed that of the three photoproducts from colchicine (CXXXII) isolated by Grewe and Wulf (100) in 1951, two are of the type already discussed. In principle, colchicine could undergo two photoisomerisations of this type, leading to compounds (CXLVI) and (CXLVII). However, structure (CXLVII) is to be preferred on the grounds of strain. Gardner and coworkers assigned the structure (CXLVII) to β - and γ -lumicolchicine, with cis and trans configurations of the C-D ring fusion with respect to the acetamido group respectively. (Scheme 55).

SCHEME 55



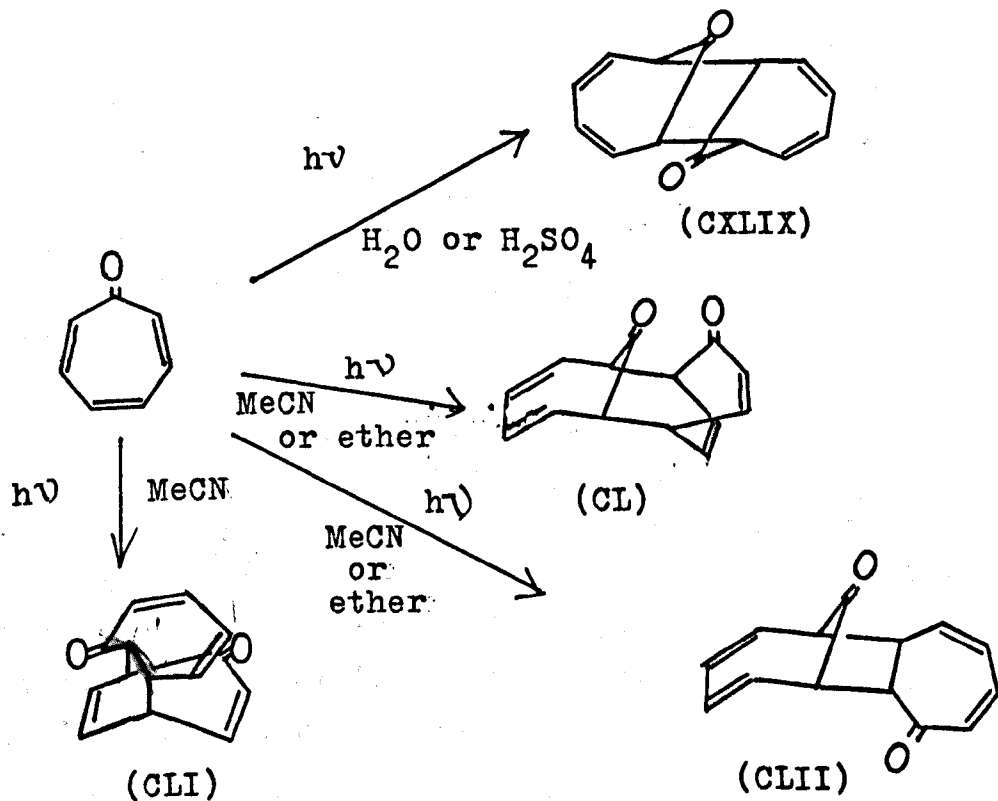
In 1969, Collington and Jones (62) reported that benz[b]tropone underwent a similar photoisomerisation to yield the tricyclic ketone (CXLVIII) and a photodimer. (Scheme 56).

SCHEME 56

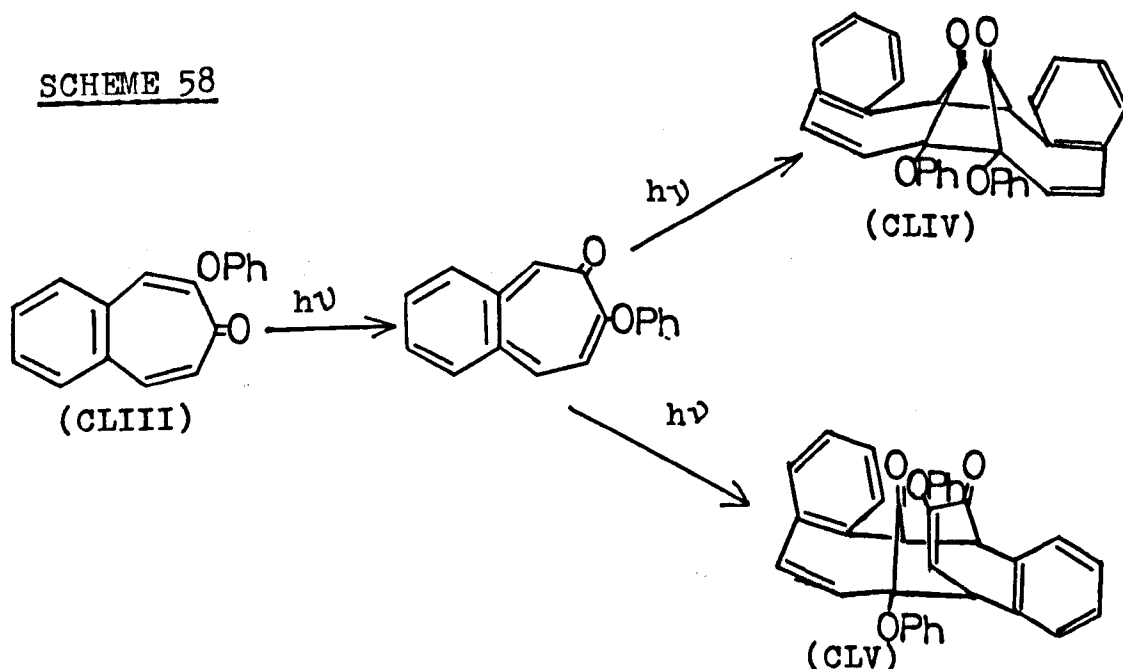


In spite of the use of a variety of solvents for the photolysis of tropone itself, to date no simple bicyclic photoproducts have been isolated. On the other hand, a large number of photodimers have been identified. (Scheme 57).

SCHEME 57

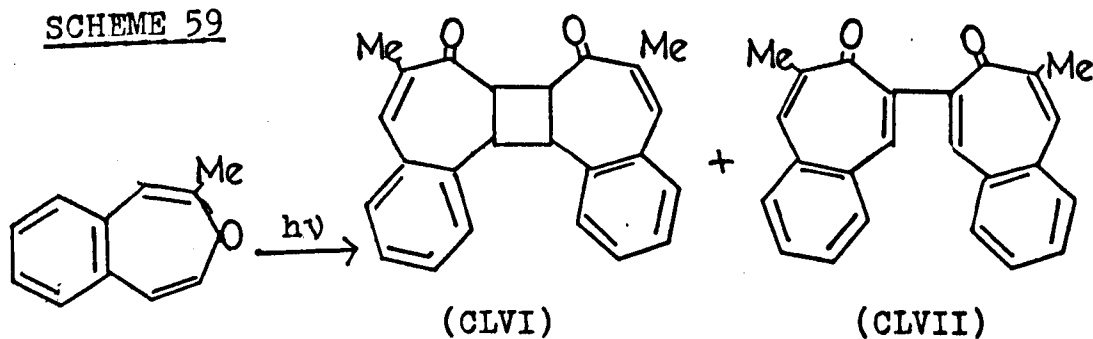


SCHEME 58



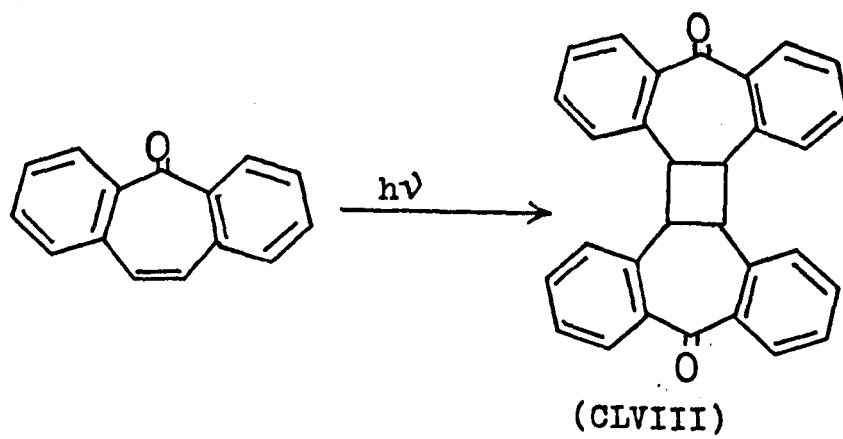
Mukai and coworkers (107) have reported that 6-methylbenz[d]tropone forms a (2+2) photodimer (CLVI) and the dehydrogenated product (CLVII). (Scheme 59).

SCHEME 59



Dibenz[2,3-6,7]tropone is also restricted in the type of photoreaction it can undergo, from considerations of the energy required to destroy the aromaticity of either of the benzene rings. It has been reported to form a (2+2) dimer (CLVIII) involving the double bond in the tropone ring not included in either of the benzene rings (108, 109). (Scheme 60).

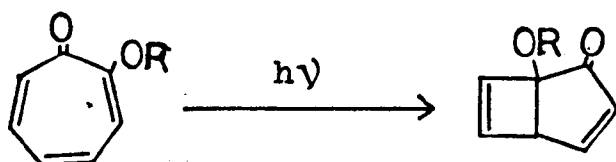
SCHEME 60



DISCUSSION

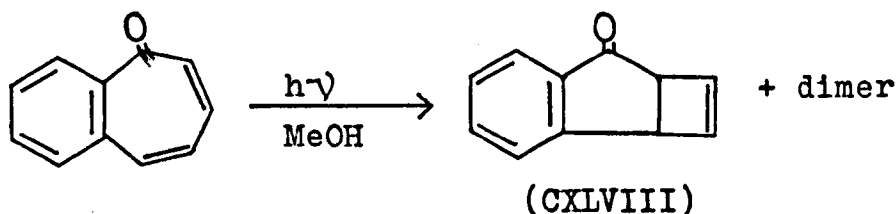
There are many instances in the literature of troponoid compounds undergoing valence isomerisations on photolysis to yield compounds containing the bicyclo[3.2.0]heptanone ring system. (Scheme 61).

SCHEME 61

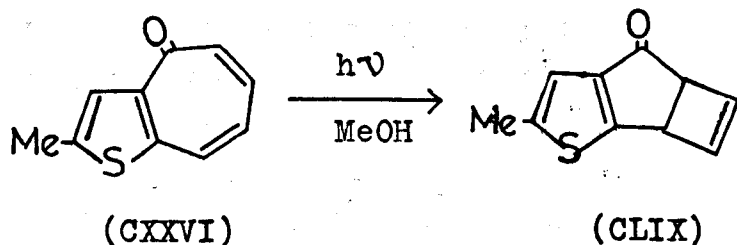


One notable exception is tropone itself, which forms a variety of dimeric compounds depending on conditions. Of particular interest is the case of benz[b]tropone which, as reported by Collington and Jones (62) in 1969, undergoes valence isomerisation on irradiation in methanol to yield 2a,7a-dihydro-cyclobut[a]inden-7-one (CXLVIII) in 13% yield, and a dimer of as yet undetermined structure. (Scheme 62).

SCHEME 62



It was anticipated that irradiation of 2-methyl-thieno[b]tropone (CXXVI) under similar conditions might lead to the formation of the analogous compound (CLIX). (Scheme 63).

SCHEME 63

Irradiation of a solution of the thienotropone in methanol followed by evaporation of the solvent led to a gum which was separated by p.l.c. (50% benzene-chloroform mixture, three elutions) into six bands. The two major bands (each representing 29% of the total weight of material on the plates) were shown to be a photodimer and unchanged starting material. In a subsequent photolysis, the infrared absorption spectrum of the mixture before chromatography was measured; the only absorption in the "carbonyl region" occurred at 1670 cm^{-1} . The cyclobutindenone formed on photolysis of benzotropone has an absorption maximum at 1704 cm^{-1} , whilst the dimer formed in the same reaction has an absorption maximum at 1671 cm^{-1} . The absence of any absorption around 1700 cm^{-1} in the photolysis products of 2-methylthienotropone clearly indicates that the anticipated photovalence isomerisation does not occur under the conditions used here. Varying the duration of the photolysis for periods between three and twenty-four hours was found to have little effect on the reaction beyond altering the yield.

It is virtually impossible to restrict on theoretical grounds the type of photodimer which might be formed in this reaction, in view of the fact that

the literature contains examples of (6+6), (6+4), (6+2) and (4+2) photodimers of tropone, and also an example of a (2+2) photodimer from dibenz[b,f]tropone. However, it seems unlikely that 2-methylthieno[b]-tropone would form a dimer involving 6π electrons, as to do so would destroy the aromaticity of the thiophen ring with a consequent decrease in stability. It seems equally unlikely that a (2+2) dimer will be formed in this reaction, in view of the fact that such a dimer has been reported only for dibenz[b,f]tropone, in which any dimer involving 4 or 6π electrons would destroy the aromaticity of one or both of the benzene rings. It seems, therefore, that the photodimer formed here will have been formed from (4+2) cycloaddition; possible structures are shown in fig. 5.

The 220 MHz spectrum of the dimer is shown in fig. 6; the signals at τ 5.6, 6.2, 6.95 and 7.1-7.25 p.p.m. may be attributed to protons attached to carbon atoms occupying bridgehead positions; those at τ 3.3, 3.5. and 3.75-3.9 p.p.m. to alkene protons. The singlets at τ 2.73 and τ 2.92 p.p.m. are due to the protons attached to the thiophen rings, and that at τ 7.60 p.p.m. is due to the two methyl groups.

The INDOR (Internuclear Double Resonance) scanning technique was used to determine which protons are coupled, and also to separate the overlapping signals of the two proton multiplet at τ 3.75-3.90 p.p.m.

The INDOR technique involves monitoring the intensity of one line in the signal of an individual proton whilst sweeping a perturbing field through the remainder of the spectrum. The monitoring signal used

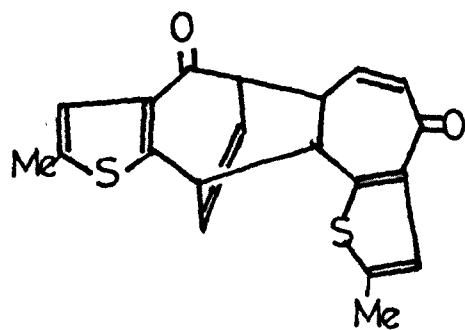
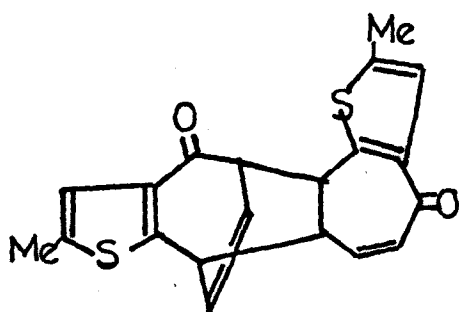
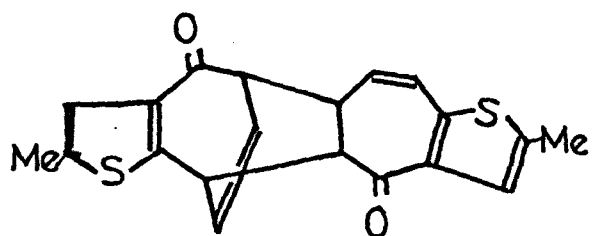
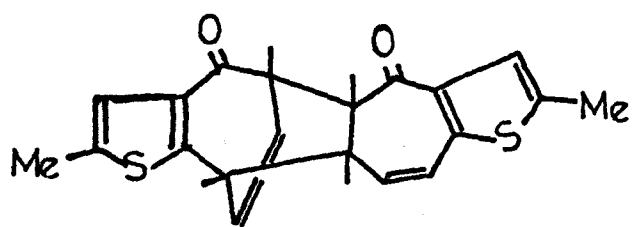


Figure 5

must be of low intensity to produce a significant
 proton whose signal is being measured by the
 INDOE spectrum.

In a simple AX system of two
 doublets, the energy level diagram is shown in
 fig. 7.

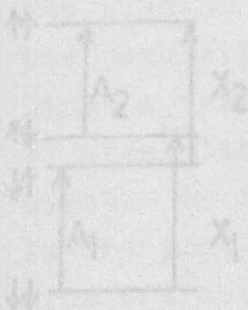
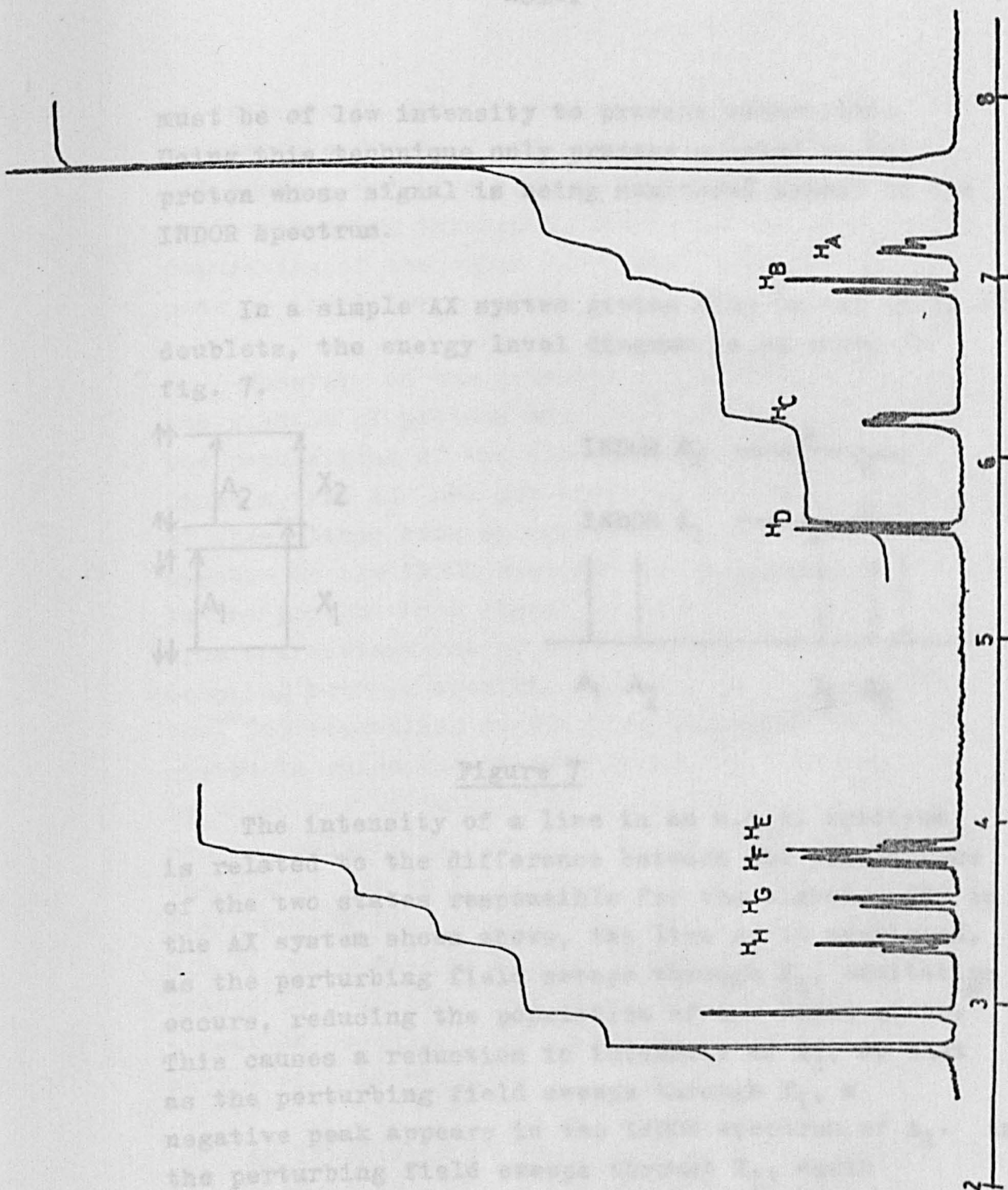


Figure 7

The intensity of a line in an NMR spectrum
 is related to the difference between the
 of the two states. In a simple AX system, the
 the AX system shows two lines, one positive
 as the perturbing field sweeps through the
 occurs, reducing the population of the upper level.
 This causes a reduction in the intensity of the
 as the perturbing field sweeps through the
 negative peak appears in the NMR spectrum of the
 the perturbing field sweeps through the
 excitation occurs, but in this case the
 population of the upper level is increased.
 results, causing a positive signal to be observed
 of this line. Conversely, if the line is negative,
 as the perturbing field sweeps through the

Fig. 6 N.m.r. spectrum of photodimer



must be of low intensity to prevent saturation. Using this technique only protons coupled to the proton whose signal is being monitored appear in the INDOR spectrum.

In a simple AX system giving rise to two pairs of doublets, the energy level diagram is as shown in fig. 7.

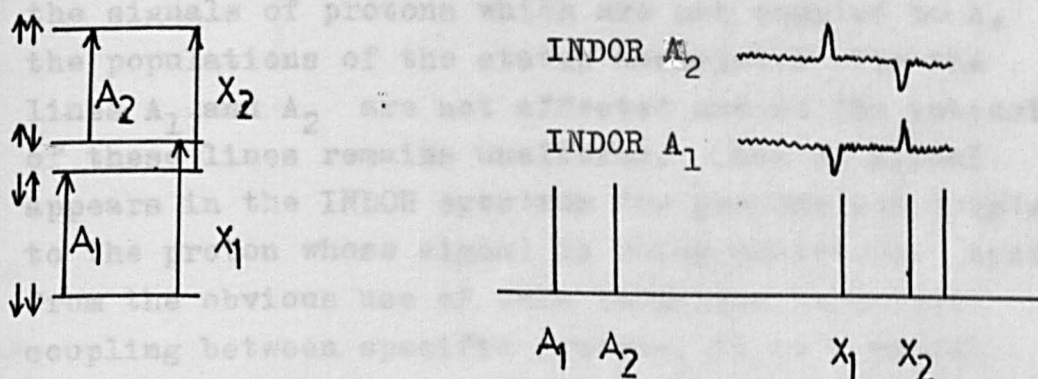


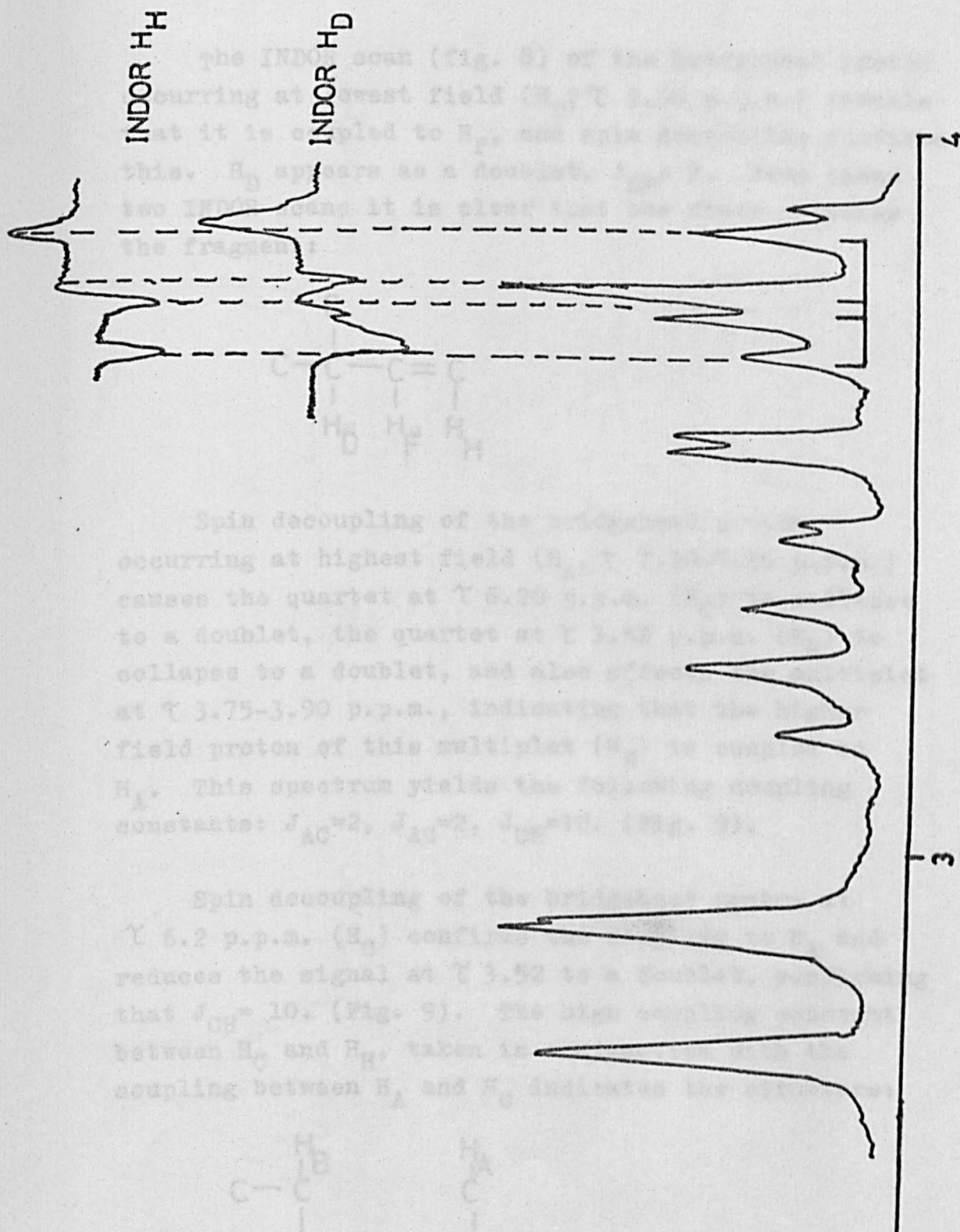
Figure 7

The intensity of a line in an n.m.r. spectrum is related to the difference between the populations of the two states responsible for the signal. If, in the AX system shown above, the line A_1 is monitored, as the perturbing field sweeps through X_1 , excitation occurs, reducing the population of the lower state. This causes a reduction in intensity of A_1 , so that as the perturbing field sweeps through X_1 , a negative peak appears in the INDOR spectrum of A_1 . As the perturbing field sweeps through X_2 , again excitation occurs, but in this case a decrease in the population of the upper level responsible for A_1 results, so that the intensity of A_1 increases, causing a positive signal in the INDOR spectrum of this line. Conversely, if the line A_2 is monitored, as the perturbing field sweeps through X_1 , there is

an increase in the population of the lower level responsible for A_2 , causing an increase in intensity and hence a positive peak in the INDOR spectrum, whilst sweeping through X_2 causes an increase in the population of the upper level and hence a negative peak in the INDOR spectrum.

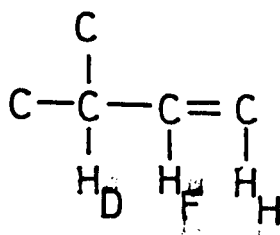
However, as the perturbing field sweeps through the signals of protons which are not coupled to A, the populations of the states associated with the lines A_1 and A_2 are not affected and so the intensity of these lines remains unaltered. Thus no signal appears in the INDOR spectrum for protons not coupled to the proton whose signal is being monitored. Apart from the obvious use of this technique to detect coupling between specific protons, it is a useful tool for separating overlapping signals. In an ABX system in which the signals for A and B overlap, but in which only A is coupled to X, the signal due to A can be isolated by carrying out an INDOR scan in which the signal due to X is monitored; as the perturbing field sweeps through the overlapping signals of A and B, peaks will appear in the spectrum as the field sweeps through the lines of A, but no signal will appear on sweeping through the lines of B. Hence only A will be observed.

An INDOR scan of the alkene proton occurring at lowest field (H_H , ~ 3.3 p.p.m.) shows that it is coupled to one of the protons in the two proton multiplet which occurs at ~ 3.75 - 3.90 p.p.m; the coupling is with the proton occurring at lower field (H_H , $J_{HF} = 6$) and reveals that the signal is a quartet. (Fig. 8).



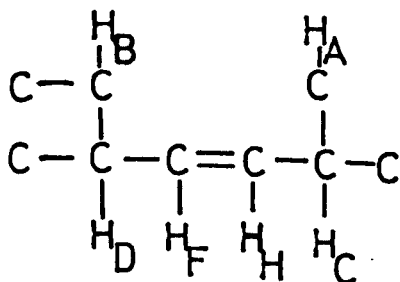
INDOR Spectrum of photodimer - Fig. 8

The INDOR scan (fig. 8) of the bridgehead proton occurring at lowest field (H_D , τ 5.60 p.p.m.) reveals that it is coupled to H_F , and spin decoupling confirms this. H_D appears as a doublet, $J_{DF} = 8$. From these two INDOR scans it is clear that the dimer contains the fragment:



Spin decoupling of the bridgehead proton occurring at highest field (H_A , τ 7.10-7.25 p.p.m.) causes the quartet at τ 6.20 p.p.m. (H_C) to collapse to a doublet, the quartet at τ 3.52 p.p.m. (H_G) to collapse to a doublet, and also affects the multiplet at τ 3.75-3.90 p.p.m., indicating that the higher field proton of this multiplet (H_E) is coupled to H_A . This spectrum yields the following coupling constants: $J_{AC} = 2$, $J_{AG} = 2$, $J_{CH} = 10$. (Fig. 9).

Spin decoupling of the bridgehead proton at τ 6.2 p.p.m. (H_C) confirms the coupling to H_A and reduces the signal at τ 3.52 to a doublet, confirming that $J_{CH} = 10$. (Fig. 9). The high coupling constant between H_C and H_H , taken in conjunction with the coupling between H_A and H_C indicates the structure:



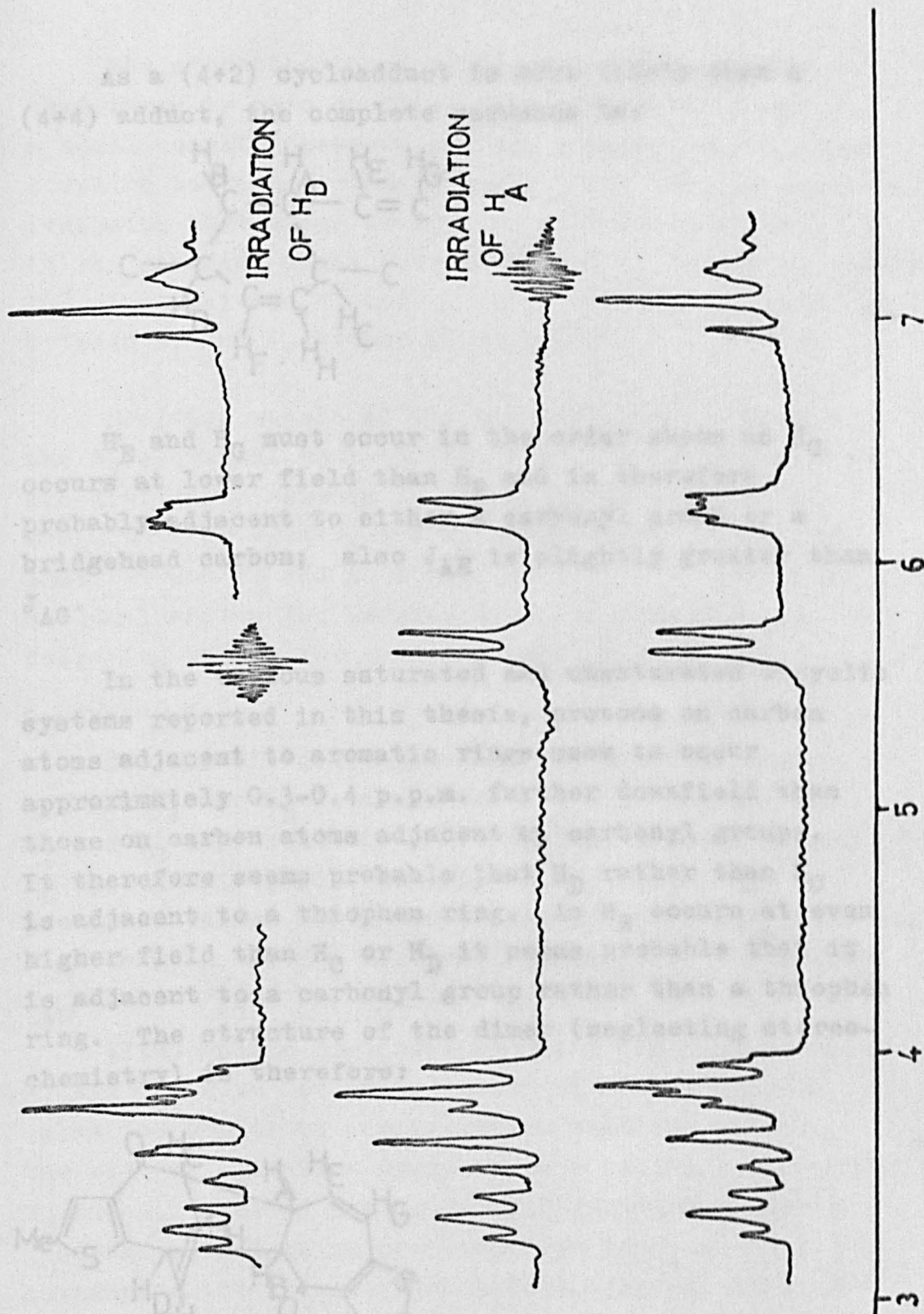
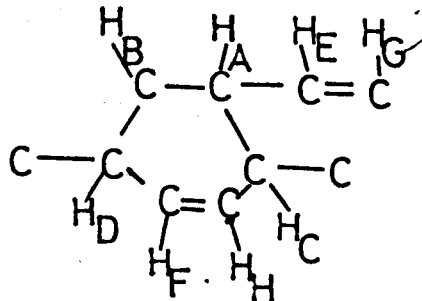


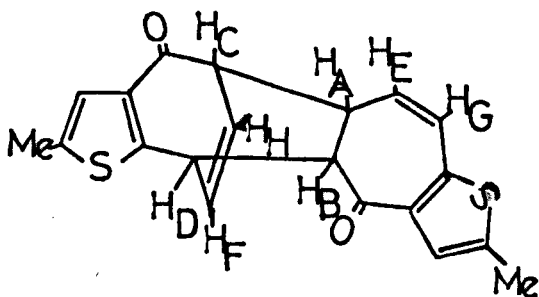
Fig. 9

As a (4+2) cycloadduct is more likely than a (4+4) adduct, the complete sequence is:



H_E and H_G must occur in the order shown as H_G occurs at lower field than H_E and is therefore probably adjacent to either a carbonyl group or a bridgehead carbon; also J_{AE} is slightly greater than J_{AG} .

In the various saturated and unsaturated bicyclic systems reported in this thesis, protons on carbon atoms adjacent to aromatic rings seem to occur approximately 0.3-0.4 p.p.m. further downfield than those on carbon atoms adjacent to carbonyl groups. It therefore seems probable that H_D rather than H_C is adjacent to a thiophen ring. As H_B occurs at even higher field than H_C or H_D it seems probable that it is adjacent to a carbonyl group rather than a thiophen ring. The structure of the dimer (neglecting stereochemistry) is therefore:

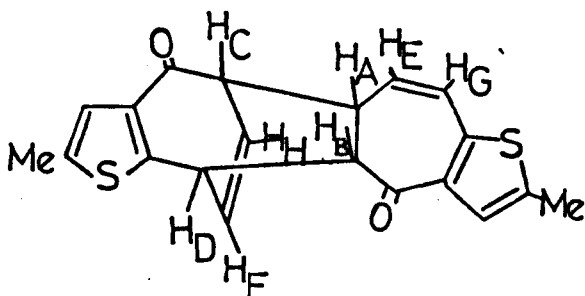


The stereochemistry of the molecule must be such that there is zero coupling between protons B and D, a small coupling between protons A and C, and a large coupling between protons A and B. The Karplus equation indicates that these conditions will be fulfilled if the dihedral angle between H_B and H_D is approximately 90° , that between H_A and H_C close to 90° , and that between H_A and H_B either 0° or 180° .

Dreiding models of the cis and trans isomers of the dimer reveal that in the trans configuration the dihedral angle between H_A and H_B is approximately 180° , that between H_A and H_C approximately 90° , and that between H_B and H_D approximately 60° . For these dihedral angles the Karplus equation predicts the following values for coupling constants: $J_{AB}=11$, $J_{AC}=0$, $J_{BD}=2$.

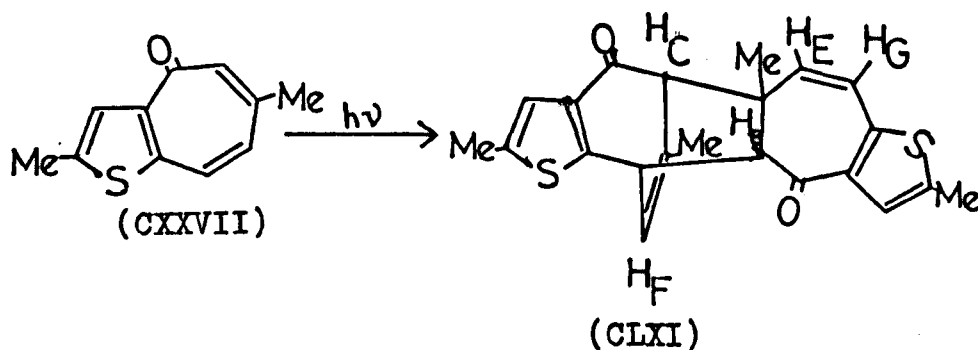
For the cis configuration, the dihedral angle between H_A and H_B is approximately 0° , that between H_A and H_C approximately 60° , and that between H_B and H_D approximately 90° , leading to the following predicted values for the coupling constants: $J_{AB}=8.5$ hz, $J_{AC}=2$ hz, $J_{BD}=0$. The observed coupling constants are: $J_{AB}=11$ hz, $J_{AC}=2$ hz, $J_{BD}=0$.

Although the predicted coupling constant between H_A and H_B is in better agreement with the observed value for the trans configuration than for the cis, the cis configuration predicts zero coupling between H_B and H_D , whereas the trans configuration predicts that there will be no coupling between H_A and H_C . Although neither isomer leads to predicted coupling constants which agree exactly with the observed values, the cis isomer seems to be in slightly better agreement than the trans. Thus it would appear that the structure of the dimer is:



Photolysis of 2,6-dimethylthieno[b]tropone (CXXVII) should help to clarify the situation, assuming that it leads to formation of the analogous dimer (CLXI). (Scheme 64).

SCHEME 64



In the new dimer H_A and H_H would be replaced by methyl groups; thus there would be only three bridgehead protons, confirming that addition takes place across C5 and C6 of the molecule, rather than across C7 and C8. The signal due to H_C should appear as a singlet, thus confirming that H_C rather than H_D

is adjacent to the carbonyl group, and confirming that the dimer is "head-to-tail" rather than "head-to-head". The signal due to H_B should also appear as a singlet, unless the methyl group at the bridgehead position alters the stereochemistry sufficiently to make J_{BD} non-zero. The signals due to H_E , H_F and H_G should appear as doublets in the new spectrum. Unfortunately, it seems unlikely that the n.m.r. spectrum of the new dimer will resolve the uncertainty about the stereochemistry of the bridgehead positions.

EXPERIMENTAL

Preliminary Notes

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

Infrared absorption spectra were measured on a Perkin-Elmer 257 spectrophotometer, either in solution (e.g. CHCl_3) or as Nujol mulls (mull).

Electronic absorption spectra were recorded on a Unicam SP 800 instrument; the figures in brackets following the position of absorption maxima are $\log_{10} \epsilon$.

Nuclear magnetic resonance spectra are measured either at 60 MHz on a Perkin-Elmer R10 instrument, or at 220 MHz on a Varian instrument. The INDOR spectra are measured at 90 MHz on a Perkin-Elmer R32 instrument. The chemical shifts are quoted in 'tau' (τ) from an internal tetramethylsilane standard (10.0 τ), and coupling constants are quoted in Hz. The following abbreviations are used: s=singlet, d=doublet, tr=triplet, q=quartet, m=multiplet.

Microanalyses were carried out on an F. & M. carbon/hydrogen/nitrogen analyser at the University of Keele.

Mass spectra were determined on an Hitachi-Perkin Elmer RMU 6 instrument.

Preparative layer chromatography (p.l.c.) was carried out on 40 x 20 cm glass plates coated with a 1.5 mm layer of Kieselgel PF₂₅₄. The separated components, visualised under ultraviolet light, were isolated by scraping off the silica and extracting several times with hot methanol. The filtered methanolic solution was evaporated to leave a residue which contained some silica. This residue was then dissolved in chloroform, dried, filtered and evaporated.

40-60 petrol refers to petroleum ether having a boiling point range 40-60°.

Unless otherwise stated, the meltingpoints/boiling points of known compounds are taken from the same source as the experimental details.

Photolysis of 2-methyl-4H-cyclohepta[3,2-b]thiophen-4-one (CXXVI)

A solution of 2-methyl-4H-cyclohepta[3,2-b]-thiophen-4-one (1 g) in methanol (1 l) was irradiated by a Hanovia medium pressure lamp through a pyrex filter under an atmosphere of nitrogen for 12 h. Removal of the solvent yielded a red gum. This was separated by p.l.c. (benzene: chloroform 1:1, 3 elutions) into six fractions:

<u>Band</u>	<u>Weight of fraction</u>	<u>%age</u>
1 (least polar)	34 mg	7
2	17	4
3	138	29
4	51	11
5	138	29
6	96	20

Band 5 was shown to consist of starting material. Recrystallisation of the material from band 3 from benzene/40-60 petrol yielded a colourless solid, m.p. 195-6°.

I.r. (CHCl₃) 1670 cm⁻¹ (-CO-)

U.v. (EtOH) 229 (4.40), 246 (sh), 266 (sh),
325 nm (3.63)

N.m.r.(CDCl₃)^τ 2.72 p.p.m. 1H (s) proton on thiophen ring
 2.90 1H (s) proton on thiophen ring
 3.30 1H (tr, J_{HF}=6, J_{CH}=10) H_H
 3.52 1H (q, J_{AG}=2.5, J_{EG}=10) H_G
 3.75-3.90 2H (m, J_{EG}=10, J_{AE}=3, J_{DF}=8, J_{FH}=6) H_F and H_E
 5.60 1H (d, J_{DF}=8) J_D

6.20 1H (q, $J_{CH}=10$, $J_{AC}=2$) H_C
6.95 1H (d, $J_{AB}=11$) H_B
7.10-7.22 1H (m, $J_{AC}=2$, $J_{AE}=3$,
 $J_{EG}=2.5$, $J_{AB}=11$) H_A

M.s.

352 (M^+)

The first part of the paper discusses the importance of the study of the history of the United States. It is argued that a knowledge of the past is essential for a full understanding of the present. The author then proceeds to discuss the various factors that have shaped the development of the United States, including the role of the government, the influence of the economy, and the impact of the culture.

The second part of the paper is a critical analysis of the various theories of the development of the United States. The author examines the theories of the Founding Fathers, the theories of the Progressive Era, and the theories of the New Deal. He argues that each of these theories has its own strengths and weaknesses, and that a comprehensive understanding of the United States requires a synthesis of all of them.

The third part of the paper is a discussion of the future of the United States. The author argues that the United States is facing a number of challenges, including the threat of nuclear war, the problem of environmental pollution, and the issue of social inequality. He believes that the only way to overcome these challenges is through a commitment to the principles of democracy and the rule of law.

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