

137 Topics in Current Chemistry

Organic Synthesis, Reactions and Mechanisms

With Contributions by
B. Christoph, L. Gann, J. Gasteiger, D. Ginsburg,
Ch. Hiller, M. G. Hutchings, P. Löw, G. Maas,
M. Marsili, H. Saller, K. Yuki

Organic Synthesis, Reactions and Mechanisms

With Contributions by

B. Christoph, L. Gann, J. Gasteiger, D. Ginsburg,
Ch. Hiller, M. G. Hutchings, P. Löw, G. Maas,
M. Marsili, H. Saller, K. Yuki

With 33 Figures and 26 Tables

Springer-Verlag Berlin Heidelberg New York
London Paris Tokyo

This series presents critical reviews of the present position and future trends in modern chemical research. It is addressed to all research and industrial chemists who wish to keep abreast of advances in their subject.

As a rule, contributions are specially commissioned. The editors and publishers will, however, always be pleased to receive suggestions and supplementary information. Papers are accepted for "Topics in Current Chemistry" in English.

ISBN 3-540-16904-0 Springer-Verlag Berlin Heidelberg New York
ISBN 0-387-16904-0 Springer-Verlag New York Heidelberg Berlin

Library of Congress Cataloging-in-Publication Data

Organic synthesis, reactions, and mechanisms.

(Topics in current chemistry; 137)

1. Chemistry, Organic—Synthesis. 2. Chemical reactions—Mathematical models. I. Christoph, B. II. Series.

QD1.F58 vol. 137 [QD262] 540 s [547'.2] 86-17863

ISBN 3-540-16904-0

ISBN 0-387-16904-0 (U.S.)

This work is subject to copyright. All rights are reserved, whether the whole or part of the material is concerned, specifically those of translation, reprinting, re-use of illustrations, broadcasting, reproduction by photocopying machine or similar means, and storage in data banks. Under § 54 of the German Copyright Law where copies are made for other than private use, a fee is payable to "Verwertungsgesellschaft Wort", Munich.

© by Springer-Verlag Berlin Heidelberg 1987
Printed in GDR

The use of registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

Typesetting and Offsetprinting: Th. Muntzer, GDR;
Bookbinding: Luderitz & Bauer, Berlin
2152/3020-543210

137

Topics in Current Chemistry

Editorial Board

- Prof. Dr. *Michael J. S. Dewar* Department of Chemistry, The University of Texas
Austin, TX 78712, USA
- Prof. Dr. *Jack D. Dunitz* Laboratorium für Organische Chemie der
Eidgenössischen Hochschule
Universitätsstraße 6/8, CH-8006 Zürich
- Prof. Dr. *Klaus Hafner* Institut für Organische Chemie der TH
Petersenstraße 15, D-6100 Darmstadt
- Prof. Dr. *Edgar Heilbronner* Physikalisch-Chemisches Institut der Universität
Klingelbergstraße 80, CH-4000 Basel
- Prof. Dr. *Shô Itô* Department of Chemistry, Tohoku University,
Sendai, Japan 980
- Prof. Dr. *Jean-Marie Lehn* Institut de Chimie, Université de Strasbourg, 1, rue
Blaise Pascal, B. P. Z 296/R8, F-67008 Strasbourg-Cedex
- Prof. Dr. *Kurt Niedenzu* University of Kentucky, College of Arts and Sciences
Department of Chemistry, Lexington, KY 40506, USA
- Prof. Dr. *Kenneth N. Raymond* Department of Chemistry, University of California,
Berkeley, California 94720, USA
- Prof. Dr. *Charles W. Rees* Hofmann Professor of Organic Chemistry, Department
of Chemistry, Imperial College of Science and Technology,
South Kensington, London SW7 2AY, England
- Prof. Dr. *Fritz Vögtle* Institut für Organische Chemie und Biochemie
der Universität, Gerhard-Domagk-Str. 1,
D-5300 Bonn 1
- Prof. Dr. *Georg Wittig* Institut für Organische Chemie der Universität
Im Neuenheimer Feld 270, D-6900 Heidelberg 1

Table of Contents

Of Propellanes — and Of Spirans

D. Ginsburg 1

A New Treatment of Chemical Reactivity: Development of EROS, an Expert System for Reaction Prediction and Synthesis Design

J. Gasteiger, M. G. Hutchings, B. Christoph, L. Gann,
Ch. Hiller, P. Löw, M. Marsili, H. Saller, K. Yuki. . . . 19

Transition-metal Catalyzed Decomposition of Aliphatic Diazo Compounds — New Results and Applications in Organic Synthesis

G. Maas 75

Author Index Volumes 101–137 255

Of Propellanes — and Of Spirans¹

David Ginsburg

Department of Chemistry, Technion — Israel Institute of Technology, Haifa, Israel

*'The time has come,' the Walrus said,
'To talk of many things;
Of shoes — and ships — and sealing wax —
Of cabbages — and kings —'*
Lewis Carroll, "The Walrus and the Carpenter"

Table of Contents

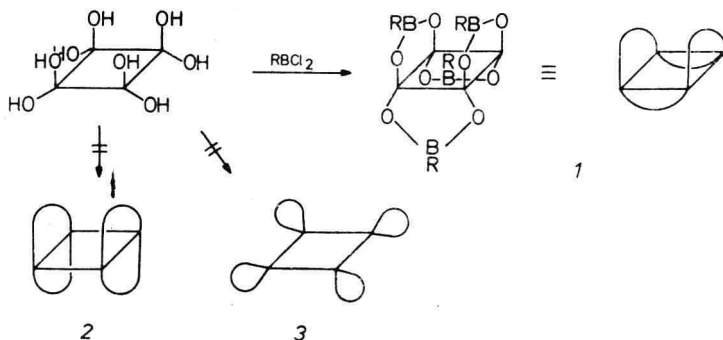
1 Introduction	2
2 Carbocyclic Propellanes and Dispirans	3
3 Heterocyclic Propellanes and Dispirans	6
4 Polyspirans	12
5 Conclusion	15
6 References	16

The synthesis of propellanes and spirans is reviewed, attempting to explain why a starting material sometimes yields a member of one class or the other, but apparently not a mixture of both.

1 Introduction

I should like to attempt to explain why a starting material that may apparently afford a propellane and/or a dispiran sometimes gives one or another, apparently not a mixture of both. There does not appear to be a denominator common for all the cases to be discussed but perhaps discussion of cases pertaining both to carbocyclic and heterocyclic compounds may cast some light on the problem; there need not be a unique reason for the behavior in the two series.

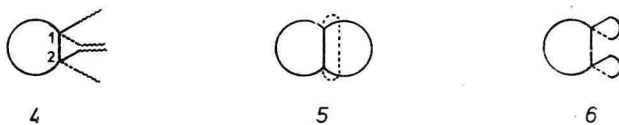
To emphasize this statement I should like to begin with a heterocyclic case which provides an outlet for the molecule's behavior that leads to neither propellane or spiran albeit, on paper, both of these types might be expected to form. In Mülheim/Ruhr the following reaction was studied:



The product *1* is formed exclusively²⁾. No propellane is formed. An explanation has been given by a group interested more in propellanes than in spirans and therefore considered only the relative stability between *1* and *2*³⁾.

MNDO calculations indicate that *1*, rather than *2*, forms because of repulsion between lone-pairs on proximate oxygens which would occur in the propellanes but not in compounds of type *1*³⁾. Compounds *1* and *3* were not compared. In the two systems which were compared, the hetero-rings are five-membered whilst in *3* they would be four-membered, perhaps sufficient reason without further ado to ignore the importance of *3* being potentially formed. The simplistic argument with respect to relatively greater strain in 4-membered rings may not be the only consideration, however. Here too electrostatic interactions between oxygens in the spiro-rings might be of even greater weight.

Often there are two (or more) courses that a reaction may take, say, cyclization of a common starting material (under whatever conditions that are being used) leading to several possible products. In this chapter, I want to discuss just such a case where cyclization of a generalized 1,1,2,2-tetrasubstituted ring *4* may lead to a propellane *5* and/or to a dispiran *6*.







It may be useful either at the outset or post factum to use molecular mechanics to calculate which of these products may be the more stable. A priori there is no way to tell whether either of the two products is the generally preferred one. In the present case such calculations do not appear to have been carried out at the outset; not surprisingly. This sort of thing was not done at the time the work was conducted. I know of only one very recent paper in which such calculations appear, comparing intermediates between a dispiran with its isomeric propellane (see below ⁴⁰⁾).

Although we are dealing with work described in the literature by means of a posteriori molecular calculation it is useful to see the relative calculated heats of formation of the isomeric propellanes and dispirans and note particularly the right-most columns so as to be in a position to gauge these against the experimental results or vice versa.

Amnon Stanger ^{3b)} has kindly calculated the heats of formation H_f and strain energies E , of the two sets of isomers shown in the Table.

Table 1. (Program MM2, QCPE No. 395)

Compound	ΔH_f (kcal/mol)	Strain Energy, E	$\Delta \Delta H_f$	ΔE
	chair 9.0	50.7	7.5	9.7
	boat 13.2	54.9		
	chair 16.5	60.4	3.1	4.4
	20.4	56.3		
	23.5	60.7		

Thus, the experimental results follow in the path of the calculations.

Incidentally, PE spectra of these dispirans in addition to several others, have been reported ^{3c)}.

2 Carbocyclic Propellanes and Dispirans

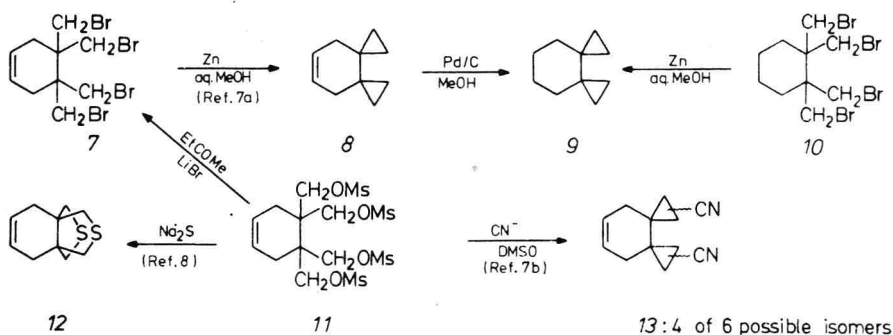
Let us now turn to simpler systems in which there are two, not three, structural alternatives for the potential product. Buchta and his collaborators published many papers on the preparation of spiro-compounds ⁴⁾. His work stemmed primarily from his greater interest in these ⁴⁾ rather than in the propellane by-products obtained in certain cases ^{4d-8)}. The case was reversed for our group. Propellanes were paramount but sometimes spiro-compounds were obtained ⁵⁾. First we shall discuss a number of carbocyclic examples.

At the time our work was done (1968) very few "small-ring" propellanes were known ⁵⁾. Nevertheless it was clear that these molecules would be strained and that

the smaller the rings the more care must be exercised in choosing the reaction conditions for the last step(s) in their synthesis; the limiting cases certainly wouldn't be formed under relatively stringent reaction conditions.

A propellane containing, say, a six-membered ring and two four-membered ones (a [4.2.2]propellane) would presumably be easier to prepare than one with three four-membered rings. This assumption was proved amply true when the time came (1971) and a [4.2.2]propellane derivative was used to prepare compounds successively containing the [3.2.2] and the [2.2.2]propellane skeleton⁶⁾.

We tried in 1968, as it turned out, unsuccessfully, to prepare a propellane having the [4.2.2] nucleus (actually it was a [4.2.2]propellene). But we were most successful in preparing the isomeric dispiran⁷⁾. None of the desired propellane was formed (see reaction scheme):



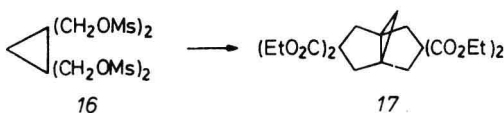
The structures of the 4 isomeric nitriles listed in the above reaction scheme were determined by NMR spectroscopy and dipole moment measurements ^{7b)}.

The tetramesylate **II** used had been reported previously^{4e,8)}. We shall see below that it nonetheless is a useful intermediate in synthesis of propellanes⁸⁾.

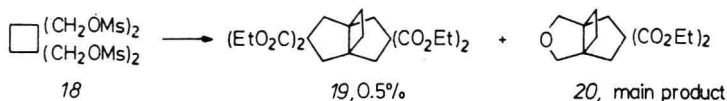
The dispiro[2.4.2.0]dec-5-ene was later used to prepare the compound with a conjugated diene in the six-membered ring⁹⁾. There is no sign of rearrangement under the conditions used.



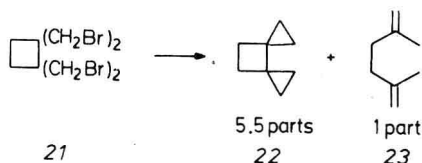
Buchta and his coworkers have contributed to the problem we are discussing. The tetraester of the [3.3.1]propellane shown, 17, is formed "überraschenderweise" from 1,1,2,2-tetrakis-hydroxymethylcyclopropane tetramesylate 16 and sodio-diethyl malonate, in 53 % yield ^{4f)}.



Wherefore “überraschenderweise”? For the corresponding cyclobutane-1,1,2,2-tetramesylate **18** gave the homologous [3.3.2]propellane tetramethyl ester **19** in only 0.5% yield, the major product being 7-oxa[3.3.2]propellane-3,3-diethyl ester **20** ^{4d}).

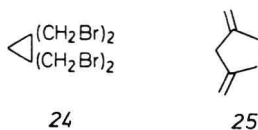


Dispiro[2.2.2.0]octane **22** was obtained in good yield along with a fragmentation product **23** by treating 1,1,2,2-tetrakis-bromomethyl-cyclobutane **21** with zinc dust in aqueous ethanol ^{4g}). The cyclobutene analog of **22** has also been reported ^{4h}).

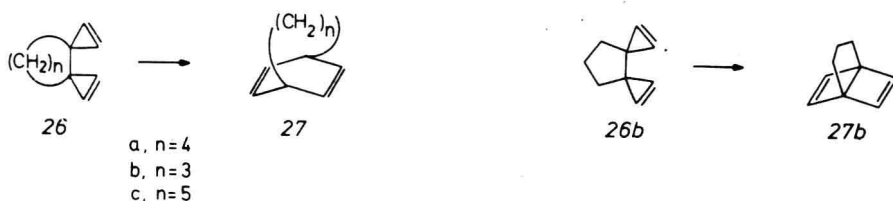


A Wurtz reaction, using sodium, of the same tetrabromide gave a wealth of fragmentation products whose formation may be reasonably explained mechanistically ^{4g}).

When the cyclopropane homolog **24**, with the same 1,1,2,2-tetrabromide array, was treated with zinc, the analogous fragmentation reaction occurred, leading in this case to an 84% yield of 2,4-dimethyl-penta-1,4-diene, **25** ^{4g}). This is in contradiction to the reaction of the corresponding tetramesylate **16** with sodio-diethyl malonate ^{4f}), (vide supra).



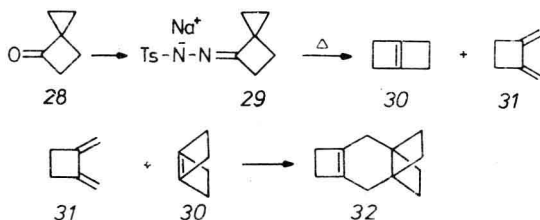
In the abovementioned cases preparation of the propellanes was direct. A very nice instance exists, however, of rearrangement of a dispiran, **26**, to Dewar benzenes **27** which happen to be [n.2.2]propelladienes. Silver ion (silver perchlorate at -20°C) promotes the isomerization, as shown ¹⁰).



Various Dewar benzenes of type 27 are formed depending upon the size of the alicyclic ring.

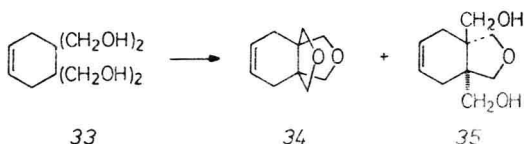
To be quite formal about the connection between spirans and propellanes an interesting pathway may be cited, although admittedly, it is farfetched.

The spiroketone 28 was converted into its tosylhydrazone whose sodium salt 29 was heated without solvent in a high vacuum. The bicyclic olefin 30 was formed and being a cyclobutene, Woodward and Hoffmann allowed it to ring-open to afford 31 and these two products were collected in a trap cooled by liquid nitrogen. When the mixture was permitted to warm up, an exothermic reaction (again allowed by W & H) set in and the cyclobuteno[4.2.2]propellane 32 was formed ¹¹.



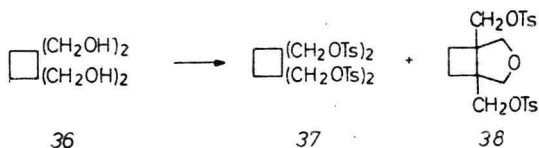
3 Heterocyclic Propellanes and Dispirans

Let us now discuss heterocyclic propellanes and dispirans. 8,11-Dioxo[4.3.3]propell-3-ene 34 was prepared (in 73% yield) by heating the tetrol 33 with KHSO_4 at 190–200 °C ^{4e}. This was accompanied by the bicyclic ether 35 (10% yield) but no

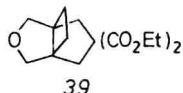


mention was made of any accompanying olefinic dispiran containing two oxetan rings. A saturated isomeric dispiran analog was prepared by another route ^{4d}. Thus, rather than form a dispiran a *trans*-fused bicyclic product is preferred.

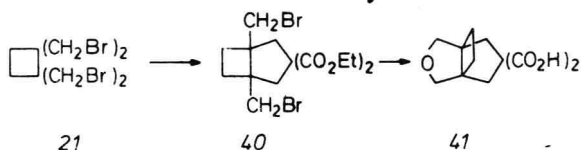
Again, only oxa-propellanes, not dispirans, were formed when 1,1,2,2-cyclobutane derivatives were used as starting materials ^{4d}. The tetratosylate 37 was formed by esterification of the corresponding tetrol 36 with *p*-TsOH accompanied by the bicyclic



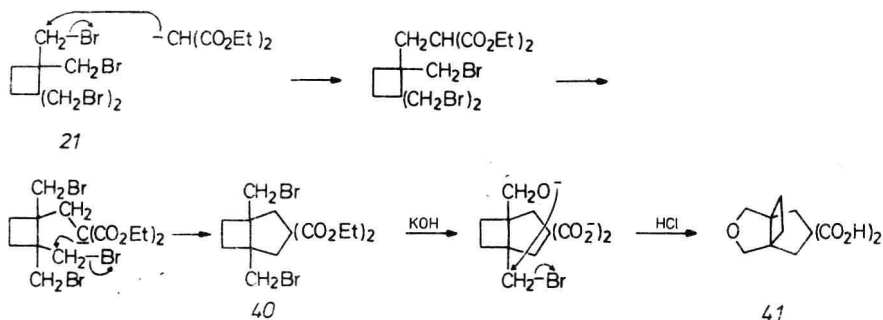
ether ditosylate 38. The tetratosylate obtained, when treated with sodio-malonic ester, did not give a [3.3.2]propellane tetraester (vide supra ^{4d}) but rather the propellane ether diester 39. This product was also obtained when the bicyclic ether ditosylate 38 was treated with sodio-malonic ester ^{4d}. Treatment of the tetrabromide 21 with



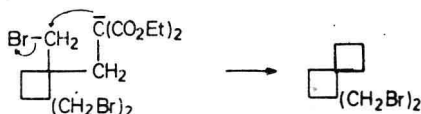
sodio-malonic ester gave the bicyclic compound 40. It gave after heating in methanol with KOH a salt which upon acidification gave the dicarboxylic acid 41. At first



glance the conditions leading to the oxa[3.3.2]propellane dicarboxylic acid may appear strange but though the reaction course is not explained one can rationalize it by stepwise nucleophilic attacks, involving one set of cis-disposed bromomethyl groups in each case:



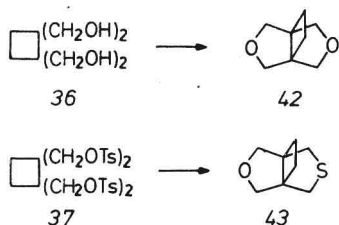
Both successive nucleophilic cyclizations to a ring are kosher because exo-nucleophilic attack is involved in each ¹². In any event one can just as easily write on paper, for example:



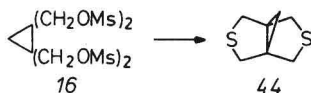
This clearly need not necessarily occur under nucleophilic conditions. But we note that in the above case, mesylate, a better leaving group is involved whilst in the present case bromide ion is the leaving group. Does one always get a propellane with the worse

leaving group and a dispiran with the better one? No, we shall see plenty of examples of propellane formation with a mesylate or a tosylate leaving group (vide infra). But here too we note that the nucleophiles being compared in the various cases differ as do the substrates, as do the strain energies of the potential propellane or dispiran products. Many parameters differ and we must recall one of the teachings of a great man when he gave the famous course on natural products: "Never compare apples with pears". This advice is useful far beyond the field of chemistry and was in fact more generally intended (as I was later told explicitly over "tea").

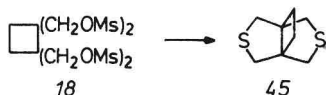
There are many more syntheses of heterocyclic propellanes from 1,1,2,2-substituted carbocyclic starting materials. The tetrol discussed above, when treated with KHSO_4 at 170–190 °C affords the dioxo[3.3.2]propellane shown; no isomeric spiran is mentioned. Although the yield is only 50%; perhaps some dispiran is hiding in the "brauner Rückstand" from which the propellane diether is either crystallized at low



temperature or sublimed? ^{4d} Heating of the corresponding tetratosylate 37 with $\text{Na}_2\text{S} \cdot 9 \text{H}_2\text{O}$ in ethanol affords the oxathia[3.3.2]propellane 43 ^{4d}. (It should be noted that in other cases dithioethers are obtained using analogous starting materials with the same sulfide.) Using the tetramesylate 16 instead of the tetratosylate 37 in dioxan/ethanol, albeit in the lower homolog (two parameters change: substrate and solvent) the dithia[3.3.1]propellane 44 is obtained in 66% yield. When DMSO is the solvent the yield of 44 rises to 72% ^{4f}.

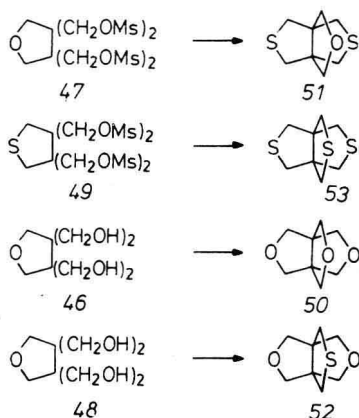


Returning to the higher member of the homologous series but nevertheless changing the sulfonate type and solvent as compared to the above case of the cyclobutane-1,1,2,2-tetratosylate 37 the corresponding tetramesylate 18 affords the dithioether 45 instead of the ether-thioether 43 (dioxan/ethanol; 77%).

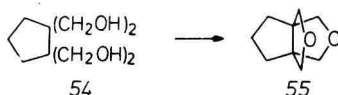


The result common to all of these cases is that apparently no dispiran is formed under these conditions, both acidic (KHSO_4) and basic (Na_2S).

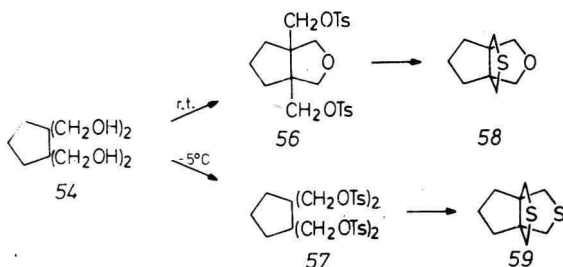
Starting from 1,1,2,2-substituted derivatives of tetrahydrofuran **46**, **47** and of thiofuran, **48**, **49**, trioxa[3.3.3]propellane **50**, oxadithia[3.3.3]propellane **51**, dioxathia[3.3.3]propellane **52** and trithia[3.3.3]propellane **53**, respectively, were obtained^{8b,c)}. No dispirans were detected!



To the Buchta heterocycles the higher homologs must also be added. The cyclopentane-1,1,2,2-substituted tetrol **54** was cyclized, in this case heated rapidly with H_2SO_4 at $160\text{--}170^\circ$, to give the dioxo[3.3.3]propellane **55** in 74% yield, no dispiran by-product being mentioned here either¹³⁾.



A somewhat different method than those described above led to dithia[3.3.3]propellane. When the same tetrol **54** was treated with *p*-TsCl in pyridine, the ditosylate **56** was formed at room temperature. At -5°C the tetratosylate **57** was formed without formation of the five-membered ether ring¹³⁾.

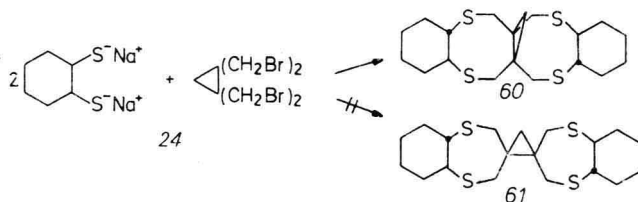


Sodium sulfide then gives products **58** and **59** of the hetero[3.3.3]propellane series; no dispirans are reported. The same approach was used for preparation of the

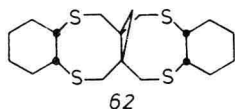
corresponding oxa-thia and dithia[3.3.1] and [3.3.2]propellanes, some reported earlier by Buchta. Somewhat different reaction conditions have been published ¹⁴⁾.

We turn now to the work of Jamrozik who has published several papers pertaining to our theme. A new and different parameter is involved. If until now we have suspected (but not proved) that a dispiran may form in lieu of a propellane with relatively small rings because of higher strain in the latter, now we must bring a set in which medium rings are involved. The relative difficulty in the formation of such rings as compared to 5- and 6-membered rings on the one hand, and the so-called large rings on the other, is too well known to require documentation.

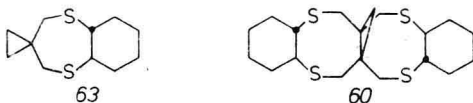
When two equivalents of *trans*-1,2-dimercaptocyclohexane are heated with the tetrabromide **24** (a substrate used earlier by Buchta ⁴⁸⁾, again *a priori* there is a possibility that a propellane **60** will form, a dispiran **61** or a mixture of both ¹⁵⁾.



Jamrozik decided between the two on the basis of what he himself regards as a tenuous argument involving UV spectroscopy. The arguments based on NMR spectroscopy support the propellane structure shown, **60**, rather than the one with a *cis*-arrangement **62** of the abovementioned hydrogens:



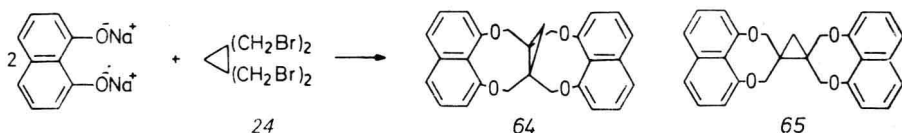
A mixture of the two is not obtained. Further mass spectral fragmentation did not show fragments based upon cleavage of the cyclopropane ring, a cleavage which is common for spirans containing such a ring, including that of the monospiran **63** (containing two sulfur atoms) shown ¹⁵⁾.



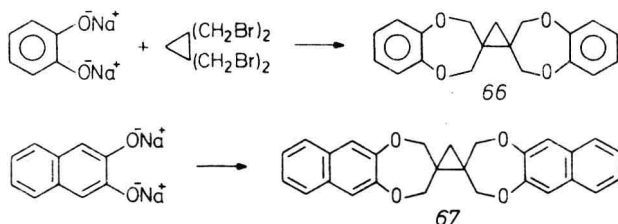
The yields of the tetrathia[6.6.1]propellane **60** and of the spirodithiabicyclo[5.4.0]-undecane **63** are only 25% and 18%, respectively. Perhaps this is the manifestation of the relative difficulty in formation of medium rings. It is not otherwise obvious why the yields should be so low. Of course propellanes with larger rings exist but the medium ring isn't cyclized at the bicyclic stage. It is already there ¹⁶⁾.

In an analogous study similar arguments were used to show that a tetraoxa[7.7.1]-

propellane **64**, and again not a dispiran **65**, is formed from the same 1,1,2,2-tetrabromomethylcyclopropane and from 1,8-dihydroxynaphthalene ¹⁷⁾.

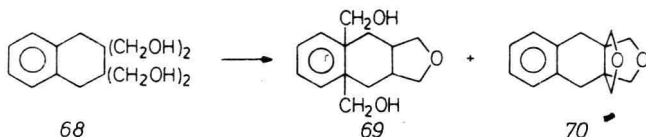


With catechol or with 2,3-dihydroxynaphthalene, dispirans of the [6.0.6.1] type are formed ¹⁸⁾:

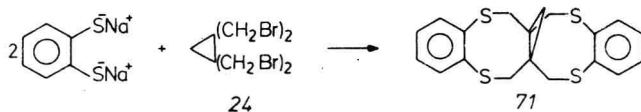


The author ¹⁷⁾ explains the difference by involving the “peri-effect” in 1,8-dihydroxynaphthalene.

Another similar case has been discussed. 2,2,3,3-Tetrahydroxymethyltetralin **68** was dehydrated by the method liked by Buchta, KHSO_4 at $170\text{--}190^\circ$, followed by sublimation. An ether **69** and a propellane diether **70** are formed in about equal amounts (4:5, respectively). Neither monospiran diol nor dispiran are formed ¹⁹⁾.



The twice aromatic analog **71** of the propellane **60** containing cyclohexane rings ¹⁵⁾ (in which there are, of course, no bridgehead hydrogens), has been obtained from the tetrabromide and 1,2-benzenedithiol. Again no dispiran is formed ²⁰⁾.



3,6,10,13-Tetrathia[6.6.1]propellane **72** has been prepared ²¹⁾. This is the parent of the dibenzo compound **71** just mentioned ²⁰⁾. The same tetrasubstituted cyclopropane **24** was used, this time simply with 1,2-ethanedithiol, under conditions of high dilution