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CYCLIZATION OF GERANIOLENE AND COMPETITIVE CYCLIZATION–CYCLIALKYLATION OF SOME PHENYL DERIVATIVES

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Abstract—The cyclization of geraniolene (**1**; 2,6-dimethyl-1,5-heptadiene) to the isomeric cyclogeraniolenes (**3**, **4**, **5**) with aqueous sulphuric acid as a catalyst proceeds partly via 2,2,6,6-tetramethyltetrahydropyran (**8**).

With phenyl- or benzyl-substituted geraniolenes a combined cyclization and intramolecular Friedel–Crafts alkylation (cyclialkylation) takes place. This leads to tricyclic systems containing cyclobutane and cyclopentane rings.

THE cyclization of geraniolene in the presence of sulphuric acid has been investigated and the results are given in Table 1, which shows that product composition strongly depends on acid concentration and reaction time.

Prolonged treatment (3 hr) of geraniolene with a tenfold weight of 65% aqueous sulphuric acid yields a mixture of α- and β-cyclogeraniolene (Exp. 1) as stated before.[1] However, when the reaction time is shortened to a few minutes (Exp. 2) the mixture contains 26% of 2,2,6,6-tetramethyltetrahydropyran[2] (cf. Fig. 1). The structure of this compound follows from its elemental analysis and its NMR spectrum, which

TABLE 1. CYCLIZATIONS OF GERANIOLENE (EXP. 1–3) AND GERANIOLENEMONOHYDRATE (EXP. 4–8) IN A TENFOLD WEIGHT OF AQUEOUS SULPHURIC ACID AT 60°C

				Product composition (%)			
Exp.	Strength H_2SO_4 %	Time min	Yield %	α + β cyclo-geraniolene (**3**, **4**)	Pyran (**8**)	Geraniolene (**1**)	Isogeraniolene (**7**)
1	65	180	60	100			
2	60	5	67	42·3	26·1	29·1	2·5
3	50	30	62	9·7	28·0	61·3	2·0
						not identified mixture of products	
4	60	5	60	2·0	95·1	2·9	
5	60	30	67	93·8	6·2		
6	50	30	58	14·6	78·9	6·5	
7	50	120	60	35·2	54·9	9·9	
8	50	15	80	9·5	83·4	7·1	

shows a singlet at 1·10 ppm representing twelve protons. Less concentrated acid (50%) and moderate reaction times tend to increase the yield of the pyran (Exp. 3).

In these experiments a fraction of the geraniolene is isomerized to 2,6-dimethyl-2,5-heptadiene ("isogeraniolene").

In Table 1, experiments starting from geraniolenemonohydrate are also listed (exp. 4–8). Under the same conditions the monohydrate invariably yields a higher percentage of pyran.

A reaction mechanism of the cyclization based on these facts is depicted in the following scheme; the γ-cyclogeraniolene **5** is not detectable in the reaction mixture but experiments in D_2SO_4–D_2O indicate its presence as a shortliving intermediate.[3] (The protons of the Me group linked to the double bond in **3** and **4** are largely exchanged for D under the conditions used in Exp. 1, indicating that the cyclic cation **2** actually is in equilibrium with the three possible cycloalkenes.)

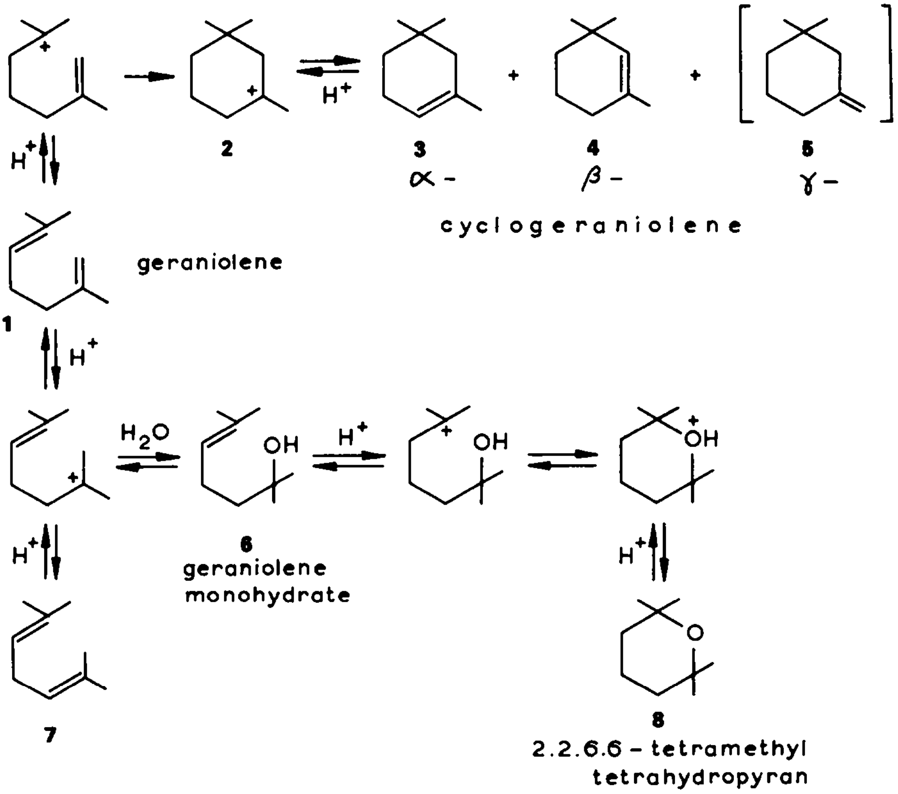

FIG. 1. Cyclization of geraniolene in 50–60%w aqueous sulphuric acid

Cyclization of 1,5(=2,6)*-dienes with a terminal phenyl group*[4]

By replacing one Me group of geraniolene hydrate by a Ph group (Cmpd **9**) the symmetry of intermediate pyrans and dienes is lost and this leads via carbonium ions to a variety of cyclic isomers as shown in Fig. 2 (cf. Table 2).

TABLE 2

Cyclization of **9** *with* H_2SO_4 *as a catalyst*

Exp.	g	H_2SO_4 96% g	Reaction conditions	10	11	12	13	14	15	16	17	18	19	20	21
				Products in distillate (average yield about 70%)											
1	5	30·0	30 g CH_3OH 20 min −20°C subs. 105 min 0°C	—	—	—	40				20	15	25		
2	5	31·5	20 g CH_3OH 120 h −20°C	—	—	—	26·7	6·3	27·1	27·8	—	12·1	—		
3	5	31·5	30 g CH_3OH 60 min 0°C subs. 60 min 57°C	—	—	—	24·8	8·1	32·5	35·6	—	—	—		
4	5	30·0*	20 g CH_3OD 60 min 0°C subs. 60 min 57°C	—	—	—	44·8	6·2	24·6	13·6	—	10·8	—		
5	2	10·4	9·6 g H_2O 60 min 60°C	12·9	11·9	47·1	8·0	3·0	11·5	5·5					
6	2	10·4	9·6 g H_2O 120 min 60°C	13·0	16·6	27·4	10·7	5·2	15·0	12·0					
7	2	12·5	7·5 g H_2O 60 min 60°C	29·2	24·4	—	17·6	8·2	11·4	9·3					

Cyclization of **9** *with* BF_3 *as a catalyst*
(yield of distillate about 20–30%)

Exp.	g	BF_3-etherate g	Reaction conditions	10	11	12	13	14	15	16	17	18	19	20	21
8	5	5	2 h reflux in 100 ml of benzene				46	24						11	19
9	5	5	3 h reflux in 50 ml of ether	51	44										
10	5	5	60 h reflux in 50 ml of ether				38	35							23
11	5	5 5	2 h reflux in 50 ml of ether Purification 14 h at 80°C without solvent											33	67

* 100% D_2SO_4.

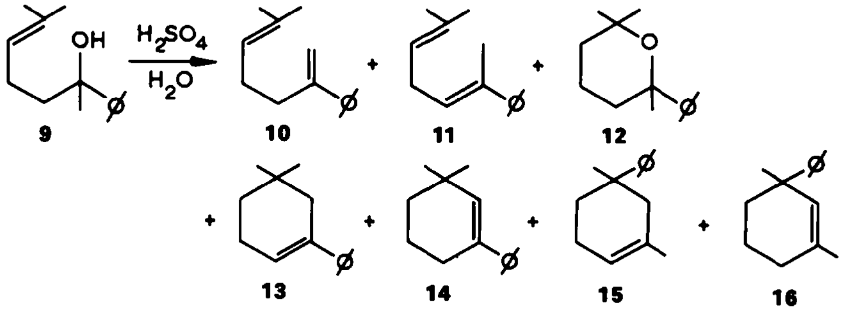

FIG. 2. The reaction of **9** with H_2SO_4aq.

The participation of relatively long living carbonium ions as intermediates for the formation of compounds **13–16** (cf. Fig. 1) is seen from the extensive deuterium incorporation, when the cyclization is carried out with $D_2SO_4/DOCH_3$.

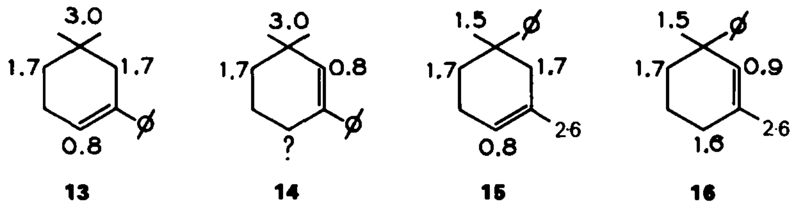

FIG. 3. Deuterium content of cyclization products obtained from **9** by treatment with 60% $D_2SO_4/DOCH_3$. (Exp. 4, Table 2).

Apart from the compounds **13–16**, formed in the presence of methanol, carbonium ions can theoretically form three ethers (**17**, **18**, **19**), which are all found experimentally.

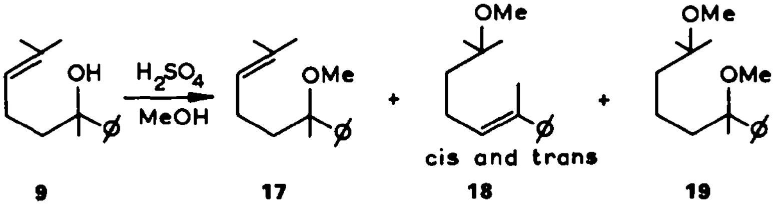

FIG. 4. Reaction of **9** in H_2SO_4/MeOH solutions.

The main interest in studying the influence of the Ph group is not in the distribution of products **13–19** (formally analogous to geraniolene) but in the potential capacity of intermediary carbonium ions to yield polycyclic products by intramolecular Friedel–Crafts reaction. Despite careful analysis no trace of such products can be isolated from reactions conducted in aqueous or alcoholic sulphuric acid. However, by heating **9** with a BF_3-ether complex as a catalyst, tricyclic **20** is isolated in low yield.*

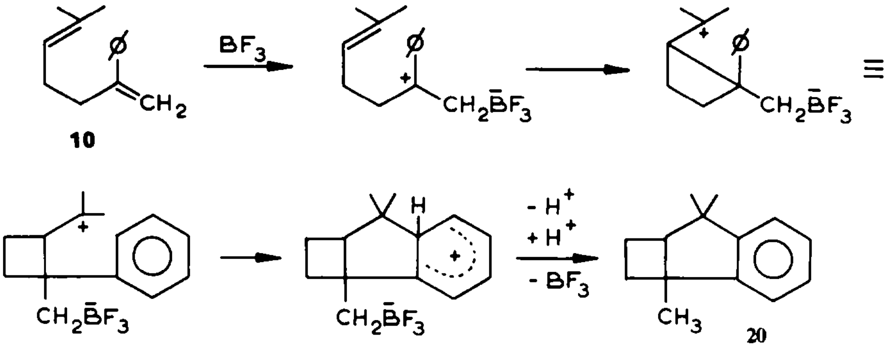

FIG. 5 Reaction of **10** with BF_3-etherate.

From the elemental analysis and the mass-spectrum of **20** the molecular formula $C_{14}H_{18}$ is obtained, the compound is therefore isomeric with **10** and **11**. The *ortho*-substitution (IR: characteristic pattern between 1700 and 2000 cm^{-1} and one single strong absorption at 755 cm^{-1}) gives a choice between a tricyclic system or a bicyclic system with a double bond.

The NMR spectrum of **20** is characterized by a singlet at 1·30 ppm representing 9 protons. No benzyl or olefinic protons are observed. All absorptions except those of the four phenyl protons are between $\delta = 1{\cdot}3$ and 2 ppm (Ref. TMS). A bicyclic structure (including one aromatic ring) with no olefinic protons and three Me groups appearing as singlets in the NMR spectrum is impossible. Only the proposed tricyclic structure **20** is in accordance with all spectral data.

In the same reaction a saturated cyclohexane derivative **21** is formed presumably by hydride transfer.

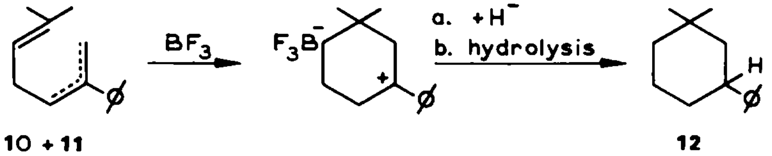

FIG. 6. The formation of 1,1-dimethyl-3-phenylcyclohexane from **10** and **11**.

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* The mechanism in Fig. 5 seems reasonable, although protons formed by reaction of borontrifluoride and traces of water may also initiate the ring closure. Because cyclization in sulphuric acid leads to other products than in BF_3-ether, we have suggested BF_3-adducts to **10** (rather than proton adducts), as possible intermediates to explain the difference.

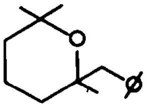
Probably the cyclization of the alcohol **9** with BF_3 yielding chiefly 6-membered rings (compds **13** and **14**, Table 2 Exp 10) is catalyzed by protons from the reaction:

$$\underset{\mathbf{9}}{\text{ROH}} \xrightarrow{BF_3} \underset{\mathbf{10},\ \mathbf{11}}{\text{Alkene}} + F_3B^{\ominus}OH + H^{\oplus}$$

The nature of the hydride donor is not known.

Products **20** and **21** are not only formed from **10** but also from its isomer **11** (reactions were usually carried out with mixtures of both isomers) and from its hydrate **9** (cf. Table 2). As far as we know tricyclic products like **20** with a 4-membered ring have never been found in comparable reactions.[5]

In order to increase chances for polycyclization phenylgeraniolene **22a*** and its hydrate **22** were subjected to similar treatment with BF_3 and found to react much faster than the unsaturated alcohol **9**. Alcohol **22** contains one CH_2 more than **9** and can therefore give rise to a tricyclic aromatic product either with two 5-membered alicyclic rings or with a condensed 4- and 6-membered ring.



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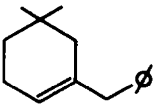

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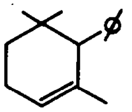

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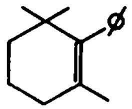

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FIG. 7. Monocyclic products obtained from **22** with BF_3 or H_2SO_4 as a catalyst.

Both products are found (**24** and **25**) together with monocyclic compounds **23**, **26**, **27** and **28** (cf. Table 3), which are logical counterparts of the monocyclic products obtained from **9**.

TABLE 3

Cyclization of **22** *with* H_2SO_4 *in* CH_3NO_2

Exp.	**22** g	H_2SO_4 96% g		Distillate g	**23**	**24** *exo*	**24** *endo*	**25**	**26**	**27**	**28**
1	5	26	24 g CH_3NO_2 15 min −20°	3	60	10		—	30		
2	5	26	24 g CH_3NO_2 15 min −10°	2·5	4	46		—	50		
3	5	26	24 g CH_3NO_2 15 min 0°	2	—	66		—	34		

Cyclization of **14** *with* BF_3*-etherate*

	22 g	BF_3-etherate g									
4	5	5	45 min at refluxing temp.	2·5	—	39	21	29	11	—	—
5	5	5	45 min at 100°	2·5	—	35	23	22	10	6	—
6	5	5	240 min at 90°	2·5	—	13		10	16	26	35

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* Formula **22a** represents one of several isomeric olefins which are present in the starting material.

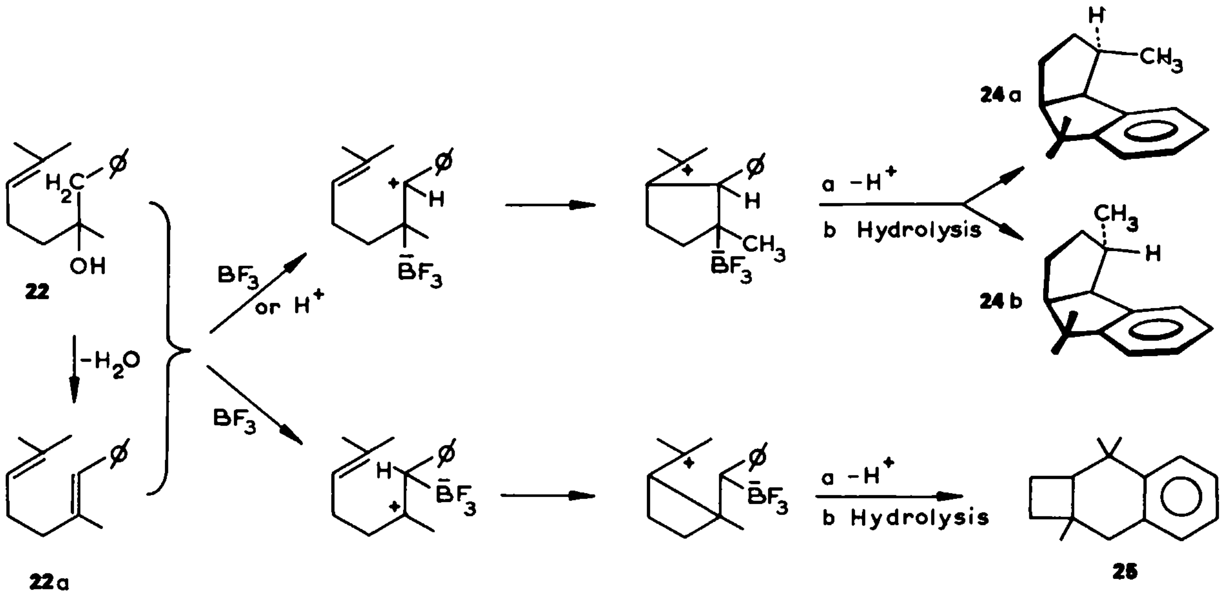

FIG. 8. Reaction of **22** and **22a** with BF_3-etherate. With H_2SO_4 the BF_3-group in intermediate carbonium ions is replaced by H.

By GLC-analysis product **24** can be separated in two isomers **24a** and **b**, which show their stereochemical difference most clearly in the NMR spectra. Both **24a** and **24b** have one (unresolved) peak at $\delta = 1{\cdot}18$ ppm, corresponding with six protons of the *gem*-dimethyl group but the third Me group is found at different positions i.e. at $\delta = 0{\cdot}68$ for **24a** and at $\delta = 0{\cdot}90$ ppm for **24b**.

Molecular models show that in **24a** the Me group is directed *towards* the shielding aromatic ring (*endo*-position), whereas in **24b** it is directed away from it (*exo*-position).

Because two 5-membered rings are always *cis*-fused no other stereoisomers are involved. Other regions of the NMR-spectra of **24a** and **b** are very similar and are in agreement with the proposed structure (e.g. four aromatic and no olefinic protons). The IR spectra of both stereoisomers show the *ortho*-absorption pattern.

Compound **25** has an IR spectrum which is typical for an *ortho*-substituted arene in the region 1700–2000 cm^{-1}. Between 650 and 800 cm^{-1} three strong absorptions without diagnostic value are found at 705, 725 and 760 cm^{-1}. A mol wt of 200 (elemental analysis and mass spectrum), and the complete absence of evidence for an olefinic double bond points to a tricyclic structure.

In the NMR spectrum three singlets are found: at 0·95 ppm (3 protons), 1·30 ppm (6 protons) and at 2·63 ppm (2 protons). The phenyl protons form an irregular multiplet at about 7 ppm. All other protons are found between 1 and 2 ppm. The singlet of the benzyl protons is somewhat broadened (halfwidth of 4 c/s). The mass spectrum shows a relatively strong parent peak (20%), besides the basepeak (*m/e* 157) only peak *m/e* = 28 exceeds 20%. The most important degradation seems to be the loss of ethylene from the cyclobutanering:

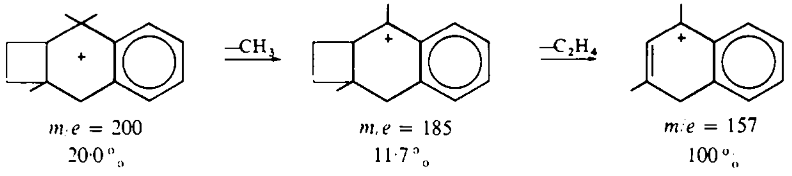

FIG. 9. Mass spectral fragmentation of **25**.

The greater ease of formation of the five-membered ring is clearly illustrated in the polycyclization of **22** by sulphuric acid in nitromethane which does not lead to **25** but only to **24a** and **b**.

A similar tendency is found in the cyclization of **9**, where sulphuric acid completely fails to direct the cyclization to **20**.

EXPERIMENTAL

Spectral and microanalytical data. The structure of Ph-substituted cyclohexenes is deduced from the IR and NMR spectra, showing a mono-substituted arene and in most cases an olefinic proton. The double bond in **28** is undetectable in this way and the UV spectrum neither shows its presence because steric factors hinder conjugation with the Ph ring.[6] The parent peak *m/e* = 200 and the mono-substitution pattern (IR, NMR) lead to the accepted structure

All other data are compiled in Tables 4 and 5 for the more interesting compounds.

TABLE 4. SPECTRAL AND MICROANAYLTICAL DATA

	21	**20**	**24a** (*exo*)	**24b** (*endo*)	**25**
IR, substitution pattern	mono	ortho	ortho		ortho
NMR, *gem*-dimethyl (ppm)	0·95 and 1·00	1·30 (sing)	1·18 (sing)		1·30 (sing)
other methyl	—	1·30 (sing)	0·90 (doubl)	0·68 (doubl)	0·95 (sing)
Mass, parent	*m/e* 188 (58·0%)	*m/e* 186 (45·1%)	*m/e* 200 (72%)		*m/e* 200 (20%)
base peak	*m/e* 91	*m/e* 157	*m/e* 159		*m/e* 157
Microanalysis					
f/th. % C	89·2/89·29	90·4/90·26	90·1/89·94		90·2/89·94
% H	10·7/10·71	9·8/9·74	10·0/10·06		9·9/10·06

TABLE 5. SPECTRAL AND MICROANALYTICAL DATA (TETRAHYDROPYRANS)

	2,2,6,6-tetra methyltetrahydropyran **8**	**12**	**23**
IR, characteristic frequencies	1015 and 1125 cm^{-1}	995 and 1080 cm^{-1}	1025 and 1121 cm^{-1}
Aromatic substitution pattern	—	mono-substitution	mono-substitution
NMR, methyl groups	four methyls at 1·10 ppm	one methyl at 0·75 ppm (caused by the axial position of the phenyl ring)	two methyls at 1·18 ppm and one at 1·16 ppm
mass, parent peak	—	*m/e* = 204 (0·11%)	—
base peak	*m/e* = 59	*m/e* = 121	*m/e* = 109
Microanalysis			
f/th. % C	76·2/76·00	83·5/82·42	82·7/82·51
% H	12·8/12·76	9·74/9·80	10·1/10·16
% 0	11·3/11·24	7·18/7·84	7·13/7·33

The instruments used were an AEI-MS2H mass spectrometer, a Varian A-60A-NMR-spectrometer and a Unicam, SP 200 IR-spectrometer.

(a) *Synthesis of the alcohols.* Compounds **6**, **9** and **22** were synthesized by reacting 2-methyl-2-hepten-6-one ("natural methylheptenone") with the Mg compounds of MeI, bromobenzene and benzylchloride, respectively, under the usual conditions.

(b) *Reactions with sulphuric acid as a catalyst* (*Tables* 1, 2 *and* 3). The H_2SO_4, diluted with the required solvent, was heated to the reaction temp. The alcohol was added dropwise with good stirring keeping the temp as constant as possible. To stop the reaction the mixture was poured into a tenfold quantity of water and then extracted with ether. The etherial soln was washed with $NaHCO_3$aq and with water, then dried over $MgSO_4$ and distilled.

(c) *Reactions with* BF_3*-etherate as a catalyst* (*Tables* 2 *and* 3). All reactions were performed by mixing the alcohols or dienes with BF_3 and keeping the temp constant. The reaction was stopped by pouring the mixture in 10% HClaq and extracting the reaction products with ether.

(d) *GLC*. The compounds were separated on preparative columns with a length of 4 m and a diam of 8 mm, with Carbowax or Apiezon-L as a stationary phase.

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