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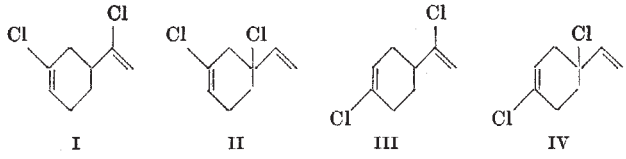
A *Cyclo*butane Derivative from Chloroprene Dimerization

Kinetic studies of the thermal polymerization of chloroprene indicate an unusual mechanism which involves formation of polymer from dimers and not from the chloroprene monomer[1,2]. The polymerization is initiated by traces of impurity in the monomer, and over a considerable range the observed rate and activation energy of polymer formation are identical with those for dimerization, indicating that the initial dimerization is the step which controls the rate in the consecutive reactions leading to polymer[3]. The characterization of the dimers and studies of the dimerization process are clearly prerequisites to understanding the mechanism of the polymerization. This communication is concerned with the initial problem of dimer separation and characterization.

It has been known for some time that chloroprene oligomerizes to form oils of low molecular weight[4], and that six- and eight-membered cyclic dimers may be isolated from these products[5–8]. Possible Diels-Alder addition compounds are shown below (I–IV), and two isomeric dichloro*cyclo*octadienes can be proposed.



I II III IV

Brown *et al.*[5] showed that six- and eight-membered ring structures were present in the dimerization products from chloroprene, but did not characterize the individual isomers. Cope *et al.*[7,8] chemically identified the products of the dimerization at 80° as structure (III) and 1 : 6 dichloro*cyclo*octa-1 : 5 diene, and structure (IV) was isolated as its dehydrochlorination product 1-chloro-4-vinyl-*cyclo*hexa-1 : 3 diene. These results were supported by the more recent work of Nazarov *et al.*[9], who in addition suggested that structure (I) is also present in dimers formed at 20° C and subsequently distilled at 90° C.

In our experiments the temperatures used in the preparation and separation of dimers have not exceeded 41° C. Products have been isolated from mixtures of two kinds, obtained as follows. (*a*) Chloroprene, which contained 1·0 per cent 1,1-diphenyl-2-picrylhydrazyl as a polymerization inhibitor, was allowed to dimerize at 35° C for 20 days, after which time the unreacted monomer was removed by high-vacuum pumping at −22° C. (*b*) Chloroprene, inhibited with 0·5 per cent *tert* butyl catechol, was allowed to dimerize at 38° C under gaseous nitric oxide for 20 days. The monomer was removed by distillation under reduced pressure of nitrogen. (We thank the Distillers Co., Ltd., for their co-operation in independently preparing this mixture.)

Fractionation of mixture (*b*) under reduced nitrogen pressure yielded two fractions, each of which accounted for about 25 per cent of the mixture. The remaining material consisted of residual monomer, high-boiling residues, and an intermediate fraction, shown by gas-liquid chromatography to be a mixture of the two main fractions. Elementary analysis of the two fractions gave results consistent with the empirical formula C_4H_5Cl (expected: C = 54·25 per cent, H = 5·65 per cent, Cl = 40·10 per cent; found for fraction 1 : C = 54·45 per cent, H = 5·59 per cent, Cl = 39·23 per cent; found for fraction 2: C = 53·02 per cent, H = 5·38 per cent, Cl = 39·70 per cent), and ebulliometric determinations[10] of the molecular weights in benzene solution indicated that the compounds were dimeric (molecular weight of fraction 1: 186 ± 5; molecular weight of fraction 2: 177 ± 5).

The boiling point of fraction 2 (40·0°–40·1°C, < 1 mm), and its infra-red and nuclear magnetic resonance spectra, showed it to be a chlorovinyl chloro*cyclo*hexene, as expected.

The infra-red spectrum of fraction 1 (boiling point 25·8–26·5°C, < 1 mm) is shown in Fig. 1. The absorption bands at 3,090, 1,642, 1,417, 987 and 927 cm^{-1} clearly indicate olefinic unsaturation, and the presence of only one sharp absorption band in the C=C stretching region suggests that the unsaturation is of a single type. Further, apart from the 927 cm^{-1} band, the set falls directly within the ranges established for the vinyl group in hydrocarbon structures, and the assignment of the set to this group is supported by the absorption in the 1,855 cm^{-1} region. The 927 cm^{-1} band lies a little on the high side of the range usually quoted for vinylic out-of-plane C—H vibrations in hydrocarbons (915–905 cm^{-1}), but this is not considered to be a serious objection to the interpretation in view of the established presence of chlorine. For the chlorine to have such an influence, it is necessary to assume that it is attached to a carbon α to the vinyl group. A striking feature of the spectrum is the absorption at 2,990 and 2,950 cm^{-1}, which contrasts with the behaviour of fraction 2, and is considerably higher in frequency than that expected for C—H stretching vibrations in six-membered rings. It is in fact much more typical of smaller (strained) ring structure, and can be accommodated without any difficulty in the range established for methylene-group vibrations in *cyclo*butane. The only direct indication of impurity in the material is a band at 1,500 cm^{-1}, which could be ascribed to traces of an aromatic component.

In the nuclear magnetic resonance spectrum (Fig. 2), the low-field bands are typical of the type-*ABC* spin system of a vinyl group not coupled to any other hydrogen nuclei. The upfield band is consistent with two pairs of mutually coupled (A_2B_2) cyclic methylenic protons. Integration of the spectrum shows the proton ratio to be three vinylic to two methylenic; that is, two vinyl groups per —CH_2 —CH_2— fragment.

Taking both infra-red and nuclear magnetic resonance spectral evidence into account, the only feasible structure for fraction 1 is 1,2-dichloro 1,2-divinyl *cyclo*butane, a compound not hitherto suspected as a principal product of chloroprene dimerization.

The mixture obtained by procedure (*a*) was separated by thin-layer chromatography on a preparative scale.

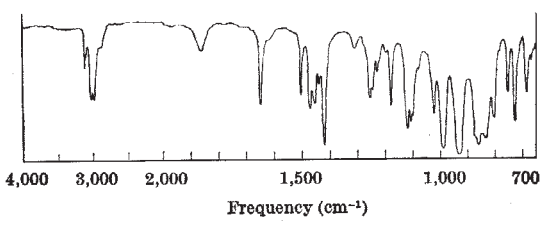


Fig. 1. Infra-red spectrum of fraction 1.

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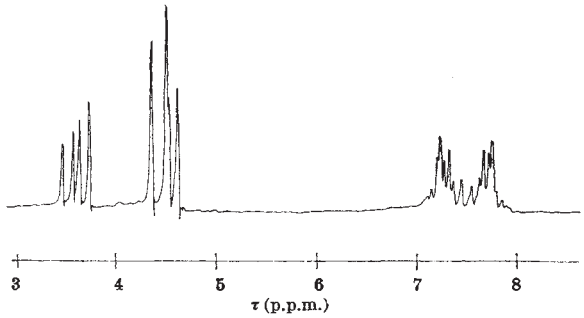
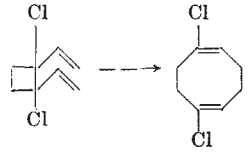


Fig. 2. Nuclear magnetic resonance spectrum of fraction 1. Chemical shifts measured with respect to tetramethyl silane, $\tau = 10$.

This was done at room temperature using *n*-hexane as eluent on silica gel '*HF*254 (Merck)' plates. (The absorbent was coated to a thickness of 1·5–2 mm, and was then activated for 3 h at 120° C. A 2 mm band of 50 mg of the mixed dimers was coated on to the plate at 40° C. The separated bands were detected by two methods: (i) irradiation with 254 mμ ultra-violet light, and (ii) the development of an edge-strip with a 2 per cent solution of perchloric acid in methanol. The bands were scraped out and then soxhlet-extracted with ether.) Two bands were observed, and approximately the same weight of product was isolated from each. The products were spectroscopically characterized as identical with fractions 1 and 2 from preparation (*b*).

Thus 1,2-dichloro 1,2-divinyl*cyclo*butane is one of the principal products of chloroprene dimerization at relatively low temperature. It is possible that the failure of other workers to isolate this compound may involve the higher temperatures previously used in the preparation or isolation of the dimers. At such temperatures the dichlorodivinyl *cyclo*butane might undergo a Cope rearrangement to form 1,6-dichloro 1,5-*cyclo*octadiene[11]. In the present work, a peak corresponding to this compound has been observed in high temperature gas chromatograms of dimer samples which have been shown spectroscopically to contain no 1,6-dichloro 1,5-*cyclo*octadiene before injection. This provides indirect evidence for the rearrangement.



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IMMUNOLOGY

Suppression of Antibody Production by Phytohaemagglutinin

The *in vitro* effect of phytohaemagglutinin (PHA) on small lymphocytes from the peripheral blood is now well known[1,2], and a limited number of studies of the effect of this substance *in vivo* have been made in man[3,4] and laboratory rodents[5–7]. Calne and his colleagues[8] reported the use of PHA to augment the immunosuppressive effect of 'Imuran'. We have studied the effect of PHA on the immune response of rats to foreign red blood cells, and the preliminary results of our experiments are reported here.

The animals used in these experiments were young Wistar albino rats of the same inbred strain weighing about 200–220 g. The PHA used was obtained from Burroughs Wellcome. The animals used were divided into several groups and were treated as follows:

Group 1. Three doses of 0·5 ml. PHA were injected intraperitoneally at 24 h intervals, followed 24 h later by 1 ml. of washed 1 per cent chicken erythrocyte suspension also injected intraperitoneally.

Group 2. These animals were given PHA as described but were not immunized with the erythrocytes.

Group 3. The animals in this group were not treated with PHA but were given an immunizing injection of chicken erythrocytes as in Group 1.

Group 4. These rats were immunized with erythrocytes as described but also received one injection of 0·5 ml. PHA 6 h later.

All animals were bled at the start of the experiment (day 0), immediately before immunization (day 3) and on the second, fourth and sixth days after immunization (that is, days 5, 7 and 9). The treated rats in Groups 1 and 2 were also bled daily during the administration of the PHA.

Complement dependent haemolytic antibodies were detected by adding 2 per cent washed chicken erythrocytes to doubling dilutions of test sera in the presence of excess complement. The serum–erythrocyte–complement mixtures were incubated at 37° C for 60 min and then examined for haemolysis. 50 per cent lysis was taken as the end point of antibody activity.

Results of a typical experiment are summarized in Table 1; other experiments have given similar results.

Table 1. HAEMOLYSIN PRODUCTION IN RATS WITH AND WITHOUT PHA TREATMENT

Day	Group 1	Group 2	Group 3	Group 4
0	–	–	–	–
1	– – – – –	– – – – –	– – – – –	– – – – –
2	– – – – 2	– – – –	– – – – –	– – – – –
3*	2 – 2 – 2	– – – 2	– – – – –	– – – – –
5	– – – – –	– – – –	– – – – –	– – – – –
7	– – – – –	– – 4; –	16; 128; 64; 64; 64	32; 8; 128; 64; 256
9	2; 4; – 32; 8	– – 8; –	128; 64; 128; 128; 64	256; 1,024; 256; 512; 1,024

Antibody production is expressed as the reciprocal of the highest dilution giving 50 per cent lysis of chicken erythrocytes.
* Immunization after the sample was taken.

Haemolytic antibody was found in low titre in a number of Group 1 animals before immunization. No activity was found on either the second or fourth day after immunization in Group 1 animals, but low titre antibody was found in most 2 days later.

In Group 2 animals also, little haemolytic antibody activity was found with the exception of low titre in one animal on the seventh and ninth days of the experiment.

Naturally occurring haemolytic antibody was not found in pre-immunization samples from Group 3 rats. No antibody was detected until the fourth day after immunization, when considerable titres were obtained in all animals, persisting until at least the sixth day after immunization.

As in Group 3, no haemolytic antibody was detectable in Group 4 until the fourth day after immunization.

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