Eighty mg. of sodium borohydride in 10 ml. of water was added in portions with occasional stirring. The *p*H was maintained at 8.0 by the addition of *N* acetic acid when necessary. The mixture was allowed to stand for three hours, acidified to *p*H 5.0 with acetic acid and 360 mg. of sorbitol was added. The mixture, after standing in the ice-box overnight, was adsorbed on a 20-ml. column of Dowex-50 (H^+ form); the column was washed with 500 ml. of water and the disaccharide displaced with 5% pyridine. The uronic acid-containing portions were combined and lyophilized; yield 310 mg.

Anal. Reducing sugar—less than 1%; uronic acid (carbazole 52%); Elson–Morgan reaction negative.

Three hundred mg. of the reduced disaccharide was treated with 10 ml. of cold 0.02 *N* methanolic HCl and allowed to stand for 60 hours at ice-box temperature. The solvent was removed *in vacuo* and the HCl removed by repeated additions and evaporations of absolute ethanol. The resulting glass was treated with 7.5 ml. of pyridine and cooled to 0°. Five ml. of cold acetic anhydride was added and the mixture shaken for one hour at 0 to 5° and 1.5 hours at room temperature. The solvent was removed *in vacuo* and the resulting sirup was taken up in hot absolute ethanol from which crystals deposited on cooling; yield 121 mg., recrystallized from ethanol, m.p. 120.5–121° (cor.), $[\alpha]^{23}D$ −21° (1, $CHCl_3$). For this compound Levene[4] cites the constants m.p. 122°, $[\alpha]^{24}D$ −21° (3.2, ethanol) and Wolfrom, *et al.*,[5] report m.p. 121–123°, $[\alpha]^{21}D$ −23° (1.8, ethanol).

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Andromedotoxin. A Potent Hypotensive Agent from *Rhododendron maximum*

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The isolation and characterization of andromedotoxin, a physiologically active agent present in leaves of *Rhododendron maximum*, is described. The nature of the oxygen-containing functional groups has been determined.

Descriptions of the toxicity of the leaves, leaf extracts, flower extracts and the honey from several species of the *Ericaceae* occur in old historical records, in agricultural bulletins, and in the chemical and pharmacological literature. The poisoning of Grecian soldiers by honey of *Rhododendron luteum* was recorded by Xenophon (*Anabasis*, Bk. IV), and the existence of a toxic agent in this plant was confirmed by Archangelsky[1] and Plugge.[2] The first systematic study was that of Eykman[3] who described under the name asebotoxin a toxic material from *Andromeda japonica*. An extensive review by Plugge[2] carried out at about the same time established the fact that comparable effects were shown by preparations isolated from leaves of several *Andromeda* species, and de Zaayer,[4] in Plugge's laboratory, later succeeded in isolating a physiologically active crystalline substance from leaves of *R. ponticum*. It was described as a neutral material, m.p. 228–229°, $[\alpha]^{12}D$ −14.2 (alc.), with a formula $C_{31}H_{51}O_{10}$. Following Plugge, it was given the name andromedotoxin. Archangelsky[1] confirmed the presence of a toxic agent in *R. ponticum* and *R. chrysanthum*, but the isolation and analysis of crystalline material was not reported again until 1921 when Hardikar[5] isolated a crystalline substance, m.p. 258°, from rhododendron leaves of unidentified species. The molecular formula was reported to be $C_{19}H_{30-32}O_6$, and the name andromedotoxin was retained by Hardikar. The optical rotation was not reported by Hardikar. Makino's investigation (of *R. hymenanthes*) gave still different results.[6] A neutral, crystalline, nitrogen-free product, m.p. 245°, was obtained. The formula of de Zaayer was supported, and the agent was renamed rhodotoxin. The most recent investigation, that of Gilfillan and Otsuki in 1938, dealt with *R. californicum*.[7] An unidentified non-toxic substance, m.p. 183.4°, was isolated,[8] but the physiological action was found to reside in a resinous fraction from which no well-defined material was isolated. There is uniform agreement in these papers that the plants in question contain an agent or agents toxic to many animal species, but the chemical data are limited in extent. The literature contains no substantial agreement on the physical properties or formulas of the materials which have been isolated, and no information about the structure of these compounds has been recorded. It is not known with certainty whether there are several agents of similar activity, or whether the same agent is present in each of the species which have been investigated.

The present study is concerned with a physiologically active substance present in leaves of *Rhododendron maximum*. It was isolated in the form of colorless needles whose melting point varied from 260 to 270° depending on the rate of heating. A change in crystal form occurred at 245–250°. The optical rotation was not widely different from that reported by de Zaayer, but the melting point behavior indicated a lack of identity with de Zaayer's andromedotoxin. The analytical data corresponded most closely to the formula of Hardikar, but the calculated carbon–hydrogen values for the de Zaayer–Makino substances fall near the same values.

Three crystalline derivatives of this substance were prepared, and the analytical data for these three derivatives and for the parent substance were

(1) K. Archangelsky, *Arch. exptl. Path. Pharmacol.*, **41**, 313 (1901).

(2) P. C. Plugge, *Arch. Pharm.*, **221**, 1, 813 (1883); **224**, 905 (1886).

(3) J. F. Eykman, *Rec. trav. chim.*, **1**, 225 (1882).

(4) H. G. de Zaayer and P. C. Plugge, *Arch. gesamte physiologie*, **40**, 480 (1886–1887).

(5) S. W. Hardikar, *J. Pharmacol. Exper. Therap.*, **20**, 17 (1922).

(6) M. Makino, *Okayama-Igakki-Zasshi*, **39**, 2099 (1927); **40**, 138 (1928); [*C. A.*, **23**, 1691, 3027 (1929)].

(7) F. A. Gilfillan and C. Otsuki, *J. Am. Pharm. Assoc.*, **27**, 396 (1938).

(8) The melting point of rhododendrin was reported by Archangelsky[1] to be 187°. It had no physiological activity.

in agreement with the formula $C_{19}H_{30}O_6$. In view of the correspondence between these data and the description given by Hardikar, the name andromedotoxin, used by Hardikar, has been retained here.

The infrared spectrum indicated that at least two hydroxyl groups and a carbonyl ester group were present in the molecule. There was no evidence of unsaturation. The substance underwent reaction with alkali to give a colorless non-crystalline neutral material. In strong acids the compound was destroyed. This instability to acids was noted by de Zaayer, Archangelsky and Hardikar, and may be due to a decomposition initiated by loss of a hydroxyl group. Carbonyl test reagents gave negative results.

The carbonyl (ester) absorption band present in the infrared spectrum of andromedotoxin was not present in the spectrum of the non-crystalline product of alkaline hydrolysis, indicating that an acyl group was removed during hydrolysis. A Duclaux determination for volatile acids was carried out, after hydrolysis of andromedotoxin, and acetic acid was identified as the acid present in the distillate. This was evidently derived from an acetyl ester group in andromedotoxin.

A reaction directed to the preparation of an isopropylidene derivative of andromedotoxin was carried out with acetone–copper sulfate. The analytical data and the infrared spectrum for the isopropylidene derivative were in agreement on several points: the ester group of andromedotoxin remained intact, one hydroxyl group was eliminated by a dehydration reaction leading to a double bond and two hydroxyl groups were converted to a ketal structure. The infrared spectrum contained an absorption band in the hydroxyl region, indicating that the remaining oxygen atom was present as an hydroxyl group. In order to study the near infrared absorption in greater detail, a sample of this substance in carbon tetrachloride solution was examined in a Beckman Model DK spectrophotometer, using an expanded wave length scale. A single strong hydroxyl band was found at 2798 mμ, indicating that one non-hydrogen bonded hydroxyl group was present in the molecule. The successful formation of an isopropylidene derivative further indicated that two hydroxyl groups of andromedotoxin were on adjacent carbon atoms.

This result indicated that andromedotoxin contained four hydroxyl groups. Acetylation and benzoylation conditions led, respectively, to monoacetylandromedotoxin and dibenzoylandromedotoxin. The infrared spectra of both of these derivatives contained hydroxyl bands.

The periodate and lead tetraacetate oxidations of andromedotoxin confirmed the conclusion indicated by the formation of an isopropylidene derivative. A 1,2-glycol structure was indicated by these results. The oxidation of an alkaline hydrolysis product of andromedotoxin was comparable to that of andromedotoxin itself, but the periodate oxidation of acetylandromedotoxin indicated that the 1,2-glycol structure was no longer present in this derivative.

These data may be summarized as follows. Present evidence indicates that the oxygen atoms of andromedotoxin are present in four hydroxyl groups and an acetylated hydroxyl group. Two of the four hydroxyl groups are on adjacent carbons which in turn are not adjacent to the carbon carrying the acetylated hydroxyl group. One of these hydroxyl groups may be acetylated more easily than the other. The remaining two hydroxyl groups are not easily esterified, and the ease with which one is eliminated suggests that one is a tertiary hydroxyl and that the other is a secondary hydroxyl. The nature of the carbon skeleton is unknown, but since there is no evidence of unsaturation it may be concluded that several fused or bridged rings are present.

The physiological effects of andromedotoxin were studied with particular regard to its potent hypotensive action.[9] The intravenous administration of 5–10 mcg./kg. of andromedotoxin to normal dogs resulted in a blood pressure reduction of 20–40%. Perhaps the most striking feature of the drug is the extraordinary similarity it shows to protoveratrine in its pharmacological actions. This similarity extends through the stimulating effect on the barostatic pressor reflex mechanism, the respiratory effects, and the emetic action. Since andromedotoxin is not an alkaloid, it is evident that the basic nitrogen group of the veratrum alkaloids is not specifically required for their physiological action. The question of whether is there a similarity in the ring systems cannot be answered at the present time.

The recognized toxicity to animals of *Rhododendron, Kalmia, Leucothoe* and *Lyonia* species indicates that the same or related compounds may be expected to occur throughout these genera. The existence of a toxic agent or agents in *K. latifolia, L. editorum* and *L. mariana* has been confirmed, and these materials are being investigated for comparison with andromedotoxin. The reported high toxicity of *Rhododendron* honey indicates that the flowers may be a particularly rich source of andromedotoxin.

Acknowledgment.—We are indebted to the Section of Plant Introduction, Agricultural Research Service, U. S. Department of Agriculture, for the collection and identification of the plant materials, and to Dr. N. C. Moran and Dr. A. P. Richardson for the pharmacological data. The instrumental work was carried out by Mrs. I. J. Siewers and Miss Fleur Bateman, and the analytical data were supplied by Dr. W. C. Alford. Technical assistance was provided by Mr. D. L. Rogerson.

Experimental[10]

Isolation of Andromedotoxin.—Leaves, stems and small branches of *Rhododendron maximum*, collected in North Carolina, were used. The average moisture content was 48%; the leaves may be extracted when fresh or after drying.

Sixty-six pounds of fresh leaves was finely chopped (rotary cutter) and extracted with 80 gallons of boiling water for 30 minutes. Throughout the extraction the *p*H was maintained at 7–7.5 by addition of warm saturated barium hydroxide solution. The combined extracts (240 gallons) from three such extractions were concentrated to 25 gallons,

(9) These studies were carried out at Emory University. The results are described by N. C. Moran, P. E. Dresel, M. E. Perkins and A. P. Richardson, *J. Pharmacol. Exper. Therap.*, **110**, 415 (1954); N. C. Moran, M. E. Perkins and A. P. Richardson, *ibid.*, **111**, 454 (1954).

(10) All melting points were taken on a Kofler stage.

the *p*H was again adjusted to 7–7.5, and 75 gallons of 95% ethanol was added. The resulting precipitate was removed by filtration and discarded. The solution was acidified with 6 *N* hydrochloric acid to a *p*H of 6.5, and concentrated to a volume of 3 gallons. An equal volume of water was added. After filtration, the mixture was again concentrated to a volume of 3 gallons.

The dark aqueous solution was subjected to continuous extraction with chloroform for 40 hours. The desired product was only slightly more soluble in chloroform than in water, and continuous extraction was needed to remove the product. The chloroform extract (usually dark green) was concentrated (steam heat) to a low volume and treated with benzene (about 100–200 ml.). The benzene was removed by distillation, and this treatment was repeated three times to ensure complete removal of water from the residue. Ethyl acetate was added (200–300 ml.), and removed by distillation (steam heat). The ethyl acetate treatment was repeated three times. The residue was allowed to stand for several days until crystallization occurred. The crude solid was triturated with chilled ethyl acetate, separated by filtration and washed well with the same solvent. A yield of 7.43 g. of crude colorless andromedotoxin resulted, m.p. 250–260°. Comparable yields (about 0.008%) were obtained on a number of extractions with material of the same origin.

The crude material was subjected to chromatography on alumina. A 5.00-g. sample was dissolved in 2 l. of ethyl acetate by warming; after cooling to room temperature the solution was passed through a column containing 400 g. of alumina (Merck, for chromatography). The initial solution was followed by 500 ml. of ethyl acetate, and the product was eluted with 1 l. of 10% methanol in ethyl acetate. Removal of the solvents gave a crystalline residue. This was treated with 100 ml. of boiling hexane. The mixture was cooled and filtered and the product was washed well with pentane. The yield was 4.31 g. of colorless needles. Recrystallization was effected from acetone–pentane, from ethyl acetate and from ethyl acetate–pentane; all solvents gave colorless needles with identical infrared spectra. The melting point varied from 258–260° to 267–270° depending on the rate of heating. Although the melt was not discolored, it was found in separate experiments that decomposition occurred at these temperatures. A change in crystal form was noted at 245–250°.

The optical rotation was $[\alpha]^{25}D$ −8.8 (*c* 2.3, EtOH).

Anal. Calcd. for $C_{19}H_{30}O_6$: C, 64.38; H, 8.53; acetyl, 11.8. Found: C, 64.21; H, 8.77; acetyl, 12.6.

The infrared spectrum[11] (Nujol mull) contained bands indicative of at least two hydroxyl groups (at 3620 and 3470 cm.$^{-1}$) and a carbonyl group (1743 cm.$^{-1}$). The latter band is due to an acetyl ester group. There was no evidence for an unsaturated system; solutions in ethanol were transparent in the ultraviolet region, and andromedotoxin did not react with hydrogen (palladium catalyst) or with bromine.

A direct determination of the molecular weight was reported by Hardikar,[1] in confirmation of a $C_{19}H_{30-32}O_6$ structure. With the compound described here, a direct method (boiling methanol) gave variable results. The analytical data for the derivatives were in agreement with the molecular formula of Hardikar and not with that of de Zaayer.[4]

Both andromedotoxin and its hydrolysis product were unstable in strongly acid solution.

Duclaux Determination.—A solution of 31.3 mg. of andromedotoxin and 500 mg. of sodium hydroxide in 50 ml. of water was heated under reflux for one hour. After cooling, 3 ml. of concentrated sulfuric acid was added. The resulting red solution was distilled to collect 35 ml. of distillate. This sample was redistilled, and three 10-ml. portions were collected. The relative amounts of acid in the distilled portions were determined by titration with 0.02 *N* sodium hydroxide (indicator, phenol red).

In duplicate determinations the percentage acidity values were 24.8, 25.2 and 58.6, 58.8, respectively, for 10 ml. and 20 ml. These values are expressed in terms of the total acid concentration in 30 ml. of distillate, and correspond to acetic acid values determined by the same procedure.

Acetylandromedotoxin.—A mixture of 5.0 g. of andromedotoxin, 50 ml. of acetic anhydride and 2 g. of anhydrous potassium acetate was heated on a steam-bath for 1 hour, with occasional shaking. The cooled mixture was added to 200 ml. of ice-water, and after 2 hours the product was extracted with six 25-ml. portions of chloroform. The chloroform extracts were combined and washed with sodium bicarbonate solution and with water. The solution was decolorized (Norit) and dried (magnesium sulfate) and the solvent was removed. The residual sirup was dissolved in warm acetone and a little hexane was added. A 4.1-g. yield of crystalline material, m.p. 236–240°, was obtained.

Four recrystallizations gave colorless needles, m.p. 246.5–247°, $[\alpha]^{20}D$ −2.40 (*c* 1.25, chloroform, 4-dm. tube).

Anal. Calcd. for $C_{21}H_{32}O_7$: C, 63.61; H, 8.14. Found: C, 63.70; H, 8.47.

The infrared spectrum[11] (Nujol mull) showed hydroxyl bands at 3640 and 3480 cm.$^{-1}$ and a single carbonyl ester band at 1738 cm.$^{-1}$.

Dibenzoylandromedotoxin.—A solution of 100 mg. of andromedotoxin in 12 ml. of pyridine and 3 ml. of benzoyl chloride was heated (steam) for 30 minutes. After cooling, 150 ml. of 10% sodium carbonate solution was added and the mixture was allowed to stand for 24 hours. The product was extracted with 1:1 ether–ethyl acetate, and the extract was washed well with sodium bicarbonate solution, with water and dried. Removal of the solvents gave 93 mg. of crude semi-solid product. This was decolorized in benzene–methanol, and the product was allowed to crystallize in colorless form, m.p. 225–227°. Recrystallization from benzene–methanol gave an analytical sample, m.p. 226.5–227.5°.

Anal. Calcd. for $C_{32}H_{38}O_8$: C, 70.44; H, 6.81. Found: C, 70.27; H, 6.78.

The infrared spectrum[11] (Nujol mull) showed an hydroxyl band at 3480 cm.$^{-1}$ and carbonyl ester bands at 1720, 1708 and 1690 cm.$^{-1}$.

Isopropylideneanhydroandromedotoxin.—A mixture of 1.75 g. of andromedotoxin, 400 ml. of acetone and 75.0 g. of anhydrous copper sulfate was heated under reflux for 12 hours. The solids were removed and the solvent evaporated (steam) to yield a red oily product. The crude material was purified by chromatography on alumina (Merck). It was placed on a column with pentane and the product was eluted with benzene to give 0.65 g. of solid, m.p. 175–195°. Repeated recrystallization from benzene–hexane gave colorless prisms, m.p. 208–210°.

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.55; H, 8.35.

The infrared spectrum[11] (chloroform) contained an hydroxyl band (at 3640 cm.$^{-1}$) and retained the carbonyl ester band of andromedotoxin (at 1735 cm.$^{-1}$). A band indicative of carbon–carbon unsaturation was present at 1638 cm.$^{-1}$.

An examination of the near infrared spectrum in carbon tetrachloride solution, using a Beckman DK spectrophotometer, showed a single strong hydroxyl band. Under conditions of maximum resolution the peak was located at 2798 mμ; there was no secondary absorption indicative of hydrogen bonding.

Methylation Studies.—Attempts were made to methylate andromedotoxin by three procedures. The reagents were diazomethane, methyl sulfate–sodium hydroxide, and methyl iodide–silver oxide. In no case was a well-defined product isolated. The Purdie–Irvine method resulted in partial methylation; after repeated applications of methylation conditions a colorless product was obtained which did not melt sharply and which showed hydroxyl bands in the infrared spectrum.

Hydrolysis of Andromedotoxin.—A solution of 3.0 g. of andromedotoxin and 15 g. of sodium hydroxide in 135 ml. of water and 30 ml. of ethanol was heated under reflux for 2 hours. The cooled mixture was treated with a slurry of 100 g. of Amberlite IRC-50 in water. After stirring for 30 minutes, the resin was separated and the aqueous solution was concentrated under reduced pressure (steam heat); a residue of 2.40 g. of colorless amorphous solid was obtained.

Numerous attempts were made to obtain this hydrolysis

(11) These spectra have been deposited as Document number 4301 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document number and by remitting in advance $1.25 for photoprints, or $1.25 for 35 mm. microfilm, by check or money order payable to: Chief, Photoduplication Service, Library of Congress.

product in crystalline form. A variety of solvents were tried for recrystallization without success, but it was found that treatment with methyl acetate or ethyl acetate gave a crystalline substance. These products contained solvent of crystallization and a constant analysis could not be obtained. The product from ethyl acetate (colorless plates, m.p. 225–257°) showed a carbonyl ester band in the infrared. The solvated products were not studied in greater detail. Acetylation of the non-crystalline product to yield acetylandromedotoxin was not successful.

Periodate Oxidation Studies.—A study of the periodate oxidation of andromedotoxin in buffered solution (acetic acid–sodium acetate) at *p*H 4.7 was carried out,[12] using 0.0885 g. of andromedotoxin with 50 ml. of 0.0100 *M* sodium metaperiodate solution.

A consumption of 0.61 mole of periodate per mole of compound resulted after 45 minutes. The oxidation stopped at 0.70 mole after 1.5 hours.

(12) E. L. Jackson, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 361.

The same oxidation method was applied to the amorphous hydrolysis product of andromedotoxin and to acetylandromedotoxin, and in these cases the addition of ethanol was necessary. The hydrolysis product used 0.36 mole of periodate in 50 minutes, and the oxidation was complete at 0.70 mole after 4 hours. With acetylandromedotoxin, a consumption of 0.04 mole of periodate resulted after 22 hours.

Lead Tetraacetate Oxidation Studies.—The oxidation of andromedotoxin (0.1768 g.) in acetic acid solution (100 ml. of total volume) with lead tetraacetate solution (50 ml. of 0.1 *N* solution) was followed at 20°. The lead tetraacetate used in the oxidation was 0.65, 0.89, 0.93 and 1.1 moles for periods of 18 minutes, and 4, 18 and 29 hours, respectively.

Dehydrogenation Studies.—Catalytic dehydrogenation (Pd catalysts) under relatively mild conditions (up to about 250°) did not result in the formation of recognizable aromatic products. Selenium dehydrogenations at elevated temperatures gave low yields of non-crystalline material.

BETHESDA, MARYLAND

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Some Chlorine Derivatives of Norbornane (Bicyclo[2.2.1]heptane)

BY JOHN D. ROBERTS,[1a] FREDERICK O. JOHNSON AND RUDOLPH A. CARBONI[1b]

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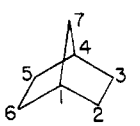
The *endo-cis* and *trans*-5,6-dichloronorbornenes were prepared by the respective additions of *cis*- and *trans*-dichloroethylene to cyclopentadiene. The stereochemical assignments were confirmed by dipole moment studies. The *cis*-dichloride was inert to hydrolysis while the *trans* isomer was hydrolyzed to 3,5-dihydroxynortricyclene. Hydrogenation of the dichloride isomers gave the *endo-cis*- and *trans*-2,3-dichloronorbornanes. Contrary to expectations based on preferential *trans*-elimination of hydrogen halide, the saturated *cis*-dichloride appeared to dehydrohalogenate somewhat less readily than the *trans* isomer, although the reaction was slow in both cases. Both isomers gave the same dehydrohalogenation product, 2-chloronorbornene, the structure of which was confirmed by oxidation to *cis*-cyclopentane-1,3-dicarboxylic acid and hydrolysis to norcamphor. Chlorination of norbornene at −75° gave nortricyclyl chloride and *syn*-7-*exo*-2-dichloronorbornane. The structure of the latter was assigned (in preference to *exo-cis*-2,3-dichloronorbornane) because of the compound's relative inertness to dehydrohalogenating reagents. *endo-cis*-2,3-Dichloronorbornane was not readily hydrolyzed, but *trans*-2,3-dichloronorbornane and *syn*-7-*exo*-2-dichloronorbornane hydrolyzed to *anti*- and *syn*-7-*exo*-2-norborneol, respectively. The *syn*-isomer also was obtained by addition of hypochlorous acid to norbornene. The structures of the chloro alcohols were inferred from their modes of formation and oxidation to chlorine-containing dicarboxylic acids which were presumed to be, respectively, *trans*- and *cis*-2-chloro-*cis*-cyclopentane-1,3-dicarboxylic acids. These acids were different from *trans*- and *cis*-4-chloro-*cis*-cyclopentane-1,3-dicarboxylic acids obtained by oxidation of *exo*- and *endo*-dehydronorbornyl chlorides, respectively. The chloro alcohols also were oxidized to the corresponding ketones, *anti*- and *syn*-7-chloronorcamphor. The assignments of the *syn* and *anti* configurations to the ketones were confirmed by dipole moment measurements. The *syn*- and *anti*-chlorohydrins were converted by pyrolysis of their carboxylic acid esters in low yield to *syn*- and *anti*-7-chloronorbornenes. Each of the latter substances on hydrogenation gave the same compound, 7-chloronorbornane.

Until recently, very little was known about the chemistry of vicinal-*cis*-alicyclic dihalides and the present research was concerned with the synthesis of such compounds by addition of appropriately substituted ethylenes to cyclopentadiene along lines laid out by Alder and Rickert.[2] It was planned originally to study the rates and mechanisms of elimination reactions of such compounds, but, in view of the recent elegant investigations of Professor Cristol and co-workers[3] on similar substances this objective has been abandoned in favor of a more general survey of the chemistry of chlorine-substituted norbornanes[4] (bicyclo[2.2.1]heptane derivatives, I).



I

Cyclopentadiene and *cis*-dichloroethylene at 190° for 17 hours in a steel bomb gave 8–11% yields of solid *endo-cis*-5,6-dichloronorbornene (II). Some (3–4%) of lower-boiling material was isolated and shown by its infrared spectrum to be *trans*-5,6-dichloronorbornene (III). Formation of III in this reaction was due presumably to partial conversion of *cis*- to *trans*-dichloroethylene. This isomerization is known to occur under the influence of heat[5] and free-radical catalysts.[6] None of the *trans*-adduct was formed when the addition was carried out in a sealed glass tube. *trans*-5,6-Dichloronorbornene (III) was prepared in 34% yield by heating cyclopentadiene and *trans*-dichloroethylene in a steel bomb with a glass liner at 190–195° for 24 hours. The assignment of the *endo* configuration to the *cis*-dichloride was made in accordance with the Alder

(1) (a) Gates and Crellin Laboratories, California Institute of Technology, Pasadena 4, Calif.; (b) U. S. Rubber Company Predoctoral Fellow.

(2) K. Alder and H. F. Rickert, *Ann.*, **543**, 1 (1940).

(3) We are indebted to Professor S. J. Cristol for much helpful information in advance of publication.

(4) In this paper, we use the nomenclature suggested for bicyclo[2.2.1]heptane by A. M. Patterson, *Chem. Eng. News*, **30**, 930 (1952).

(5) R. E. Wood and D. P. Stevenson, THIS JOURNAL, **63**, 1650 (1941).

(6) R. E. Wood and R. G. Dickinson, *ibid.*, **61**, 3259 (1939).