2-Oxygenated 1,4,5,6,7,7-Hexachloro-5-norbornenes[1a]

WILLIAM K. JOHNSON AND VICTOR MARK

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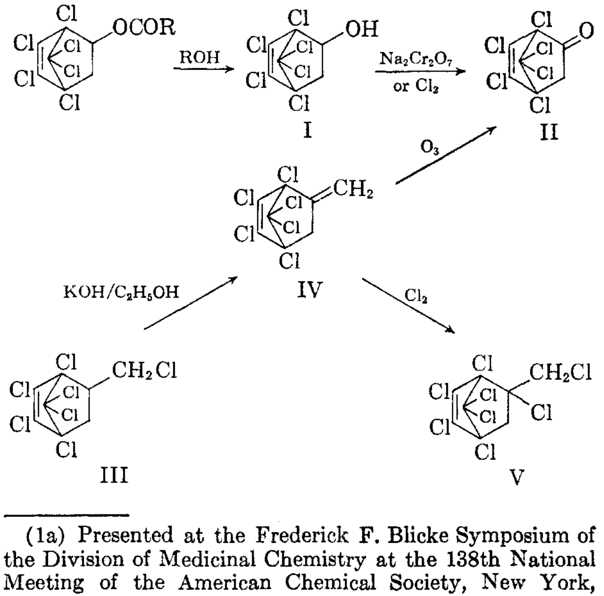
The reaction of hexachlorocyclopentadiene as a diene in Diels-Alder type reactions is well known, and reviews on this subject are available.[1b,2] The biological activity of a number of highly chlorinated compounds prompted the preparation of a few additional 2-oxygenated 1,4,5,6,7,7-hexachloro-5-norbornenes, and their characterizations are reported herein.

Only a limited number of vinyl ester adducts of hexachlorocyclopentadiene have been reported. Newman and Addor made the adduct of vinylene carbonate,[3] and several investigators have reported the vinyl acetate adduct.[4-7] We have prepared the vinyl acetate adduct in quantity as well as preparing adducts with vinyl butyrate, vinyl 2-ethylhexanoate, vinyl nonanoate, and vinyl benzoate (Table I). Generally, equimolar amounts of the diene and dienophile were heated at 180° for a period of two to six hours. The adduct of vinyl acetate and hexachlorocyclopentadiene was prepared either by heating equimolar quantities of the reactants at 180° in a sealed reactor or by introducing the vinyl acetate under the surface of the diene maintained at 180° under atmospheric pressure. Vinyl formate and isopropenyl acetate failed to form an adduct under a variety of conditions.



The vinyl ester adducts can be converted to 1,4,5,6,7,7-hexachloro-5-norbornen-2-ol (I). Esterification of I with 2-ethylhexanoyl chloride in the presence of pyridine furnished the same product as that obtained from the reaction of hexachlorocyclopentadiene and vinyl 2-ethylhexanoate. The alcohol I was oxidized to the ketone II with sodium dichromate in acetic acid or with chlorine gas. The ketone II was prepared by an alternate route which involved the dehydrochlorination of the hexachlorocyclopentadiene/allyl chloride adduct (III) with potassium hydroxide in ethanol and ozonolysis of the resulting 1,2,3,4,7,7-hexachloro-5-methylene-2-norbornene (IV). IV on chlorination yielded the octachloro compound V.

EXPERIMENTAL

1,4,5,6,7,7-Hexachloro-5-norbornen-2-ol (I). A mixture of 1,4,5,6,7,7-hexachloro-5-norbornen-2-yl acetate (179.5 g., 0.5 mole) and 1000 ml. of absolute ethanol containing 20 g. of anhydrous hydrogen chloride was heated at reflux, and the ethyl acetate formed removed by azeotropic distillation. The remaining ethanol was removed by distillation and the crude product recrystallized from hexane. There was obtained 158 g. (quantitative yield) of carbinol, m.p. 156.5–157°.

Anal. Calcd. for $C_7H_4Cl_6O$: C, 26.54; H, 1.27; Cl, 67.13. Found: C, 26.66; H, 1.39; Cl, 66.96.

The phenylurethan melted at 135° after recrystallization from 80% ethanol.

Anal. Calcd. for $C_{14}H_9Cl_6NO_2$: C, 38.56; H, 2.08; Cl, 48.78; N, 3.20. Found: C, 38.76; H, 2.16; Cl, 48.38; N, 3.40.

1,4,5,6,7,7-Hexachloro-5-norbornen-2-one (II). (a) *By oxidation of* I *with* $Na_2Cr_2O_7$. The alcohol I (35.8 g., 0.113 mole) was added during 30 min. to a well stirred mixture consisting of sodium dichromate (68.0 g., 0.23 mole), 300 ml. of water, 50 ml. of glacial acetic acid, and 500 ml. of benzene. A mild exothermic reaction was observed during the addition, and the reaction mixture was stirred for an additional 6 hr. at room temperature. The organic layer was separated, washed with water, 5% sodium hydroxide solution, and finally with water until neutral. The benzene was removed by distillation and 30 g. (84%) of crude product was obtained. The product could be distilled under reduced pressure, but solidification of the distillate in the apparatus was annoying [b.p. 105–114° (1.2–1.3 mm.)]. An analytical sample was obtained by a short path distillation at reduced pressure. It was a colorless, crystalline, but wax-like solid, m.p. 67–68°. Infrared maxima: 5.60, 6.25, 7.08, 8.07, 8.57, 8.80, 9.17, 9.43, 9.67, 10.95, 11.14, 12.00, 13.72, and 14.63 μ.

Anal. Calcd. for $C_7H_2Cl_6O$: C, 26.71; H, 0.64; Cl, 67.56. Found: C, 26.43; H, 0.88; Cl, 67.61.

(b) *By oxidation of* I *with chlorine*. Compound I (55.7 g., 0.176 mole) was dissolved in 200 ml. of carbon tetrachloride and chlorine gas passed into the mixture in the presence of a strong ultraviolet light source.[8] The addition of chlorine was terminated when the evolution of hydrogen chloride from the reaction mixture was no longer copious (visual observation). The resulting pale yellow solution was treated with charcoal, filtered, and distilled. After removal of solvent, there was obtained 31.9 g. (58% yield) of II, b.p. 105–110° (1.2 mm.). Higher boiling fractions tentatively believed to be monochlorinated II [b.p. 135–140° (1.7 mm.) n_D^{25}

(1a) Presented at the Frederick F. Blicke Symposium of the Division of Medicinal Chemistry at the 138th National Meeting of the American Chemical Society, New York, N.Y., Sept. 1960. (1b) H. E. Ungnade and E. T. McBee, *Chem. Revs.*, **58**, 249 (1958).

(2) C. W. Roberts, *Chem. & Ind.* (*London*), 110 (1958).

(3) M. S. Newman and R. W. Addor, *J. Am. Chem. Soc.*, **77**, 3789 (1955).

(4) H. Frensch and H. Goebel, German Patent Application 1,006,418.

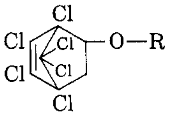
(5) E. K. Fields, *J. Am. Chem. Soc.*, **78**, 5821 (1956).

(6) P. B. Polen, U. S. Patent 2,813,914 (1957).

(7) W. K. Johnson, U. S. Patent 2,841,484 (1958).

(8) A General Electric H-100-A4 lamp was used as a light source.

TABLE I

ADDUCTS OF THE TYPE 

R	Yield, %	B.P.	Mm.	n_D^{25}	Carbon		Hydrogen		Chlorine	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
Acetyl	97	110–113	0.5	[a]	30.09	29.92	1.69	1.78	60.63	60.01
Butyryl	75	126–127	0.3	1.5224	34.14	34.06	2.61	2.56	54.96	54.88
2-Ethylhexanoyl	88	145–147	0.3	1.5084	40.66	40.39	4.10	4.02	48.01	48.17
Nonanoyl	88	176–178	1.0	1.5083	42.05	41.94	4.41	4.46	46.42	45.91
Benzoyl	71	160–163	0.2	[b]	39.96	39.85	1.92	1.96	50.52	50.32

[a] M.p. 44° (from hexane). [b] M.p. 91° (from hexane).

1.5692] which was a reddish oil and dichlorinated II [b.p. 148–152° (1.7 mm.) n_D^{25} 1.5775] which was a yellow oil were also obtained. The infrared spectra of the latter two materials are consistent with the proposed structures.

1,2,3,4,7,7-Hexachloro-5-methylene-2-norbornene (IV). A mixture of 1,2,3,4,7,7-hexachloro-5-(chloromethyl)-2-norbornene[9] (60.0 g., 0.172 mole), potassium hydroxide (9.6 g., 0.172 mole) and 500 ml. of absolute ethanol was refluxed for 9 hr. The solvent was removed by distillation at reduced pressure and the pentane soluble portion of the residue distilled. The methylene compound distilled at 104° (2 mm.) as a colorless oil n_D^{25} 1.5560 and was obtained in a yield of 95% (51.1 g.). Infrared maxima: 5.97, 6.23, 6.98, 7.07, 7.99, 8.37, 8.72, 9.22, 9.53, 9.67, 10.07, 10.36, 10.92, 11.32, 11.45, 11.79, 13.53, and 13.82 μ.

Anal. Calcd. for $C_8H_4Cl_6$: C, 30.71; H, 1.29; Cl, 68.00. Found: C, 30.97; H, 1.44; Cl, 67.65.

The olefin IV (3.2 g., 10.3 mmoles) in 90 ml. of ethyl acetate was ozonized to confirm that the double bond was exocyclic. The theoretical amount of ozone was consumed, and the ozonide was hydrogenated over a palladium on strontium carbonate catalyst[10] first at atmospheric pressure and finally in a Parr hydrogenator at 50 p.s.i.g. for 20 min. (a sample gave negative peroxide test with KI). The catalyst was separated by filtration and the ethyl acetate solution shaken out with water. The water extracts furnished a 43% yield of formaldehyde as the dimedone derivative,[11] and evaporation of the ethyl acetate yielded 2.9 g. of the ketone II (90%) whose infrared spectrum was identical with that obtained by the methods reported above.

1,2,3,4,5,7,7-Heptachloro-5-(chloromethyl)-2-norbornene. (V). A solution of IV (13.5 g., 0.0432 mole) in 30 ml. of methylene chloride was treated with chlorine in ultraviolet light until a yellow color persisted. Evaporation of the solvent left behind a colorless oil (16.2 g., 98% yield) which had n_D^{23} 1.5692. Infrared maxima: 6.21, 6.94, 7.83, 8.15, 8.21, 8.49, 8.80, 8.93, 9.24, 9.37, 9.80, 10.31, 10.82, 11.27, 11.62, 11.96, 12.45, 12.79, 13.28, 13.38, 14.12, 14.60, and 15.16 μ.

Anal. Calcd. for $C_8H_4Cl_8$: C, 25.04; H, 1.05; Cl, 73.91. Found: C, 24.80; H, 1.04; Cl, 73.16.

RESEARCH AND ENGINEERING DIVISION
MONSANTO CHEMICAL COMPANY
DAYTON 7, OHIO

ORGANIC CHEMICALS DIVISION
MONSANTO CHEMICAL COMPANY
ST. LOUIS, MO.

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Steroids. VII. Synthesis of Some 4-Azaandrostanes[1-3]

NORMAN J. DOORENBOS AND CHIEN LI HUANG[4,5]

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The synthesis of a series of 4-azacholestanes was recently described.[6] This paper reports the synthesis of a related group of 4-azaandrostanes with preliminary biological data.

17α-Methyl-4-azaandrost-5-en-17β-ol-3-one (II) was prepared (a) by refluxing the ammonium salt of 17α-methyl-3,5-seco-4-norandrostan-17β-ol-5-on-3-oic acid (I)[7] in *n*-amyl alcohol for eight hours and (b) by heating a solution of the ammonium salt of the oxo acid (I) in concentrated ammonium hydroxide in a sealed reaction vessel at 180° for six hours. The low yield by method (*a*) was shown to be due largely to the decomposition of the ammonia salt to ammonia and acid (I). 4,17α-Dimethyl-4-azaandrost-5-en-17β-ol-3-one (III) was obtained in good yield (a) by refluxing the methylammonium salt of the acid (I) in xylene and (b) by heating a solution of the acid (I) in ethanolic methylamine in a sealed reaction vessel at 140°. 4-(β-Hydroxyethyl)-17α-methyl-4-azaandrost-5-en-17β-ol-3-one (IV) and 4-benzyl-17α-methyl-4-azaandrost-5-en-17β-ol-3-one (V) were

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(1) Presented at the Frederick F. Blicke Symposium of the Division of Medicinal Chemistry at the 138th National Meeting of the American Chemical Society, New York, N. Y., September 1960.

(2) For paper VI see N. J. Doorenbos and C. P. Dorn, Jr., *J. Pharm. Sci.*, **50**, 271 (1961).

(3) Abstracted from a thesis submitted by Chien Li Huang to the graduate faculty of the University of Maryland in partial fulfillment of the requirements for the Ph.D. in Pharmaceutical Chemistry, February 1960.

(4) Sterling-Winthrop Research Fellow, 1958–1959.

(5) Present address: Research Laboratories, Spring Grove State Hospital, Baltimore 28, Md.

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