[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT LABORATORIES, UNIVERSAL OIL PRODUCTS COMPANY]

Condensation of Saturated Halides with Unsaturated Compounds. III. Condensation of Alkyl Chlorides with Polychloroölefins[1]

BY LOUIS SCHMERLING

In the second paper of this series[2] it was shown that alkyl halides may be condensed with monohaloölefins to produce dihaloalkanes, metal halides of the Friedel–Crafts type serving as catalysts. The present paper furnishes examples of the condensation of some alkyl chlorides with di- and trichloroölefins in the presence of aluminum chloride. As in the previous cases,[2,3] the reaction apparently involves the addition of the alkyl group and the chlorine atom to the double bond of the olefinic compound, the chlorine adding to the carbon atom that holds the smaller number of hydrogen atoms.

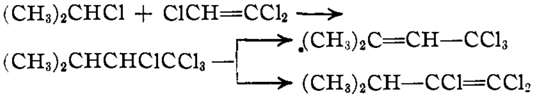
The condensation of either *n*- or isopropyl chloride with 1,2-dichloroethylene in the presence of aluminum chloride gave the same trichloropentane, presumably 1,1,2-trichloro-3-methylbutane. Intermediate isomerization of the primary propyl chloride to the secondary compound is indicated.[4] More than twice the yield of the trichloride was obtained when *cis*-dichloroethylene rather than its *trans* isomer was used.

The difference in reactivity between the *cis* and *trans* forms of the dichloroethylene was even more apparent when they were condensed with *t*-butyl chloride. Thus, 1,1,2-trichloro-3,3-dimethylbutane was obtained in up to 75% yield by the reaction with *cis*-dichloroethylene and in not more than 2% yield by the reaction with the *trans* isomer.

The fact that two different trichloroheptanes were formed by the reaction of *t*-butyl chloride with 1,2-dichloro-2-propene and with 1,2-dichloro-1-propene supports the assumption that the products were 1,2,2- and 2,2,3-trichloro-4,4-dimethylpentane, respectively. A smaller yield of product was obtained with the 1,2-dichloro-1-propene, probably because it was a mixture of the *cis*- and *trans*-isomers.

When the third dichloropropene, namely, 1,3-dichloro-1-propene was contacted with *t*-butyl chloride in the presence of aluminum chloride, a poor yield of trichloroheptane (presumably 1,2,3-trichloro-4,4-dimethylpentane and/or 1,1-dichloro 2-chloro-methyl-3,3-dimethylbutane) was obtained. The principal reaction was the dimerization of the dichloropropene to tetrachlorohexene.

Condensation of isopropyl chloride with trichloroethylene yielded tetrachloropentane together with a smaller amount of its dehydrochlorination product, trichloropentene. Since the product formed by the addition of hydrogen chloride to trichloroethylene in the presence of aluminum chloride at 50° contains 1,1,1,2- and 1,1,2,2-tetrachloroethane in the ratio of 5:1,[5] it is probable that the tetrachloropentane was chiefly 1,1,1,2-tetrachloro-3-methylbutane. The trichloropentene was either 1,1,2-trichloro-3-methyl-1-butene or 1,1,1-trichloro-3-methyl-2-butene.



$$(CH_3)_2CHCl + ClCH{=}CCl_2 \longrightarrow$$

$$(CH_3)_2CHCHClCCl_3 \begin{cases} \longrightarrow (CH_3)_2C{=}CH{-}CCl_3 \\ \longrightarrow (CH_3)_2CH{-}CCl{=}CCl_2 \end{cases}$$

Ethyl chloride could not be condensed with *cis*-dichloroethylene. The only product isolated from the reaction of these chlorides was 1,1,2-trichloroethane formed by addition of hydrogen chloride to the dichloroethylene. Similar results were observed previously[2] in an attempt to condense ethyl chloride with vinyl chloride.

Experimental

The experimental procedures will be summarized very briefly since they were similar to those previously described[2] for the analogous reactions of alkyl halides with monohaloölefins.

In Method T, the catalyst was added to the reactants in a large "test-tube" cooled to about −65° and the mixture then allowed to warm up to the reaction temperature and maintained at that point by intermittent cooling and warming, while being shaken manually. In Method B, the mixture of reactants and catalyst in a glass liner was sealed into an Ipatieff-type rotating autoclave which was then heated at the indicated temperature for four hours.

It was observed that the yield of product could often be increased (within limits) by increasing the amount of catalyst used. Thus, when 1 g. (0.03 molar proportion) of aluminum chloride was added to 26 g. each (approximately molar proportions) of *t*-butyl chloride and *cis*-dichloroethylene at −40°, little reaction occurred; the mixture was permitted to warm up to 0°, at which point the catalyst dissolved, forming an orange solution. After standing at 0 to 23° for three hours, the product was a clear red solution which on being worked up in the usual manner yielded the trichlorohexane in 21% of the theoretical yield. On the other hand, when 5 g. (0.07 molar proportion) of aluminum chloride was added to 50 g. each (approximately molar proportions) of the reactants at −65°, there was a vigorous reaction and the temperature rose to −10° in about thirty seconds and to +10° in another thirty seconds despite the fact that the reaction vessel was immersed in a Dry Ice–acetone-bath. The product was a mixture of dark red-brown liquid and white, undissolved aluminum chloride powder. The temperature dropped to −40° in a few minutes. The mixture was then maintained at −15 to −5° by intermittent warming and cooling for fifteen minutes during which time the remainder of the catalyst went

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[1] Presented before the Division of Organic Chemistry of the American Chemical Society at the Atlantic City meeting, April, 1946.

[2] L. Schmerling, THIS JOURNAL, **68**, 1650 (1946).

[3] L. Schmerling, *ibid.*, **67**, 1152 (1945).

[4] Compare reaction of *n*- and isopropyl chloride with ethylene (ref. 3).

[5] E. Mueller and C. Hoenn, *J. prakt. Chem.*, **133**, 289 (1932). See also M. S. Kharasch, S. C. Kluger and F. R. Mayo, *J. Org. Chem.*, **4**, 428 (1939), who indicate that with ferric chloride as catalyst at room temperature, the product is 1,1,1,2-tetrachloroethane.

TABLE I

CONDENSATION OF ALKYL CHLORIDES WITH POLYCHLOROÖLEFINS

Method	Reactants: Alkyl chloride RCl	g.	Chloroölefin Formula	g.	$AlCl_3$, g.	Temp., °C.	Duration, hr.	Chief product: Comp. no.	g.	%[a]	Higher-boiling, prod. g.
T	*i*-PrCl	35	*c*-CHCl=CHCl[b]	25	2	0 to 30[c]	0.1	I	26	55	1
T	*i*-PrCl	31	*t*-CHCl=CHCl[d]	40	2	0 to 23	.6	Ia	15	22	1
T	*n*-PrCl	45	*c*-CHCl=CHCl	50	6	0 to 15	.8	Ib	33	37	1
T	*t*-BuCl	50	*c*-CHCl=CHCl	50	5	−15 to +10	.3	II	73	75	2
T	*t*-BuCl	26	*c*-CHCl=CHCl	26	1	0 to 23	3.0	II	11	21	1
T	*t*-BuCl	26	*t*-CHCl=CHCl	26	2	0 to 23	5.0	II	1	2	0
T	*i*-PrCl	40	$CH_2{=}CHCl{-}CH_2Cl$[e]	55	3	0 to 18	.8	III	14	15	6
T	*t*-BuCl	49	$CH_2{=}CHCl{-}CH_2Cl$	59	3	−10 to −10	.5	IV	60	56	3
T	*t*-BuCl	50	$CHCl{=}CHCl{-}CH_3$[f]	60	3	−20 to −10	.8	V	19	18	5
T	*t*-BuCl	50	$CHCl{=}CH_2{-}CH_2Cl$[g]	60	3	−10 to −10	.5	VI	3	3	
								VIA	14	23	14
T	*i*-PrCl	25	$CHCl{=}CCl_2$	40	2[h]	0 to 20	.5	VII	27	42	0
								VIIA	12	23	
B	EtCl	10	*c*-CHCl=CHCl	20	3	22 to 40	4.0[i]	VIII	6	28	0

[a] Per cent. of theoretical based on the alkyl chloride or chloroölefin charge, much of which was usually recovered as such. Except for the relatively small amount of higher-boiling material shown in the last column, very little by-product was formed. [b] B. p., 58–60°. Prepared by the isomerization of the *trans* isomer (G. Chavanne, *C. A.*, **7**, 1180 (1913); **9**, 2898 (1915)). [c] The aluminum chloride was added to the reactants at −70° and the mixture was permitted to warm up in the usual manner. Much of the catalyst went into solution as the temperature rose to 0°; at 3° there was a sudden vigorous reaction and the temperature rose to 30° even though the test-tube was quickly immersed in a Dry Ice–acetone-bath. [d] B. p. 49°, m. p. −50 to −49°; obtained from Eimer and Amend. [e] B. p. 92–94°, obtained from Research Chemicals, Columbia, S. C. [f] B. p. 84–100°, mixture of *cis-* and *trans*-isomers. Obtained from Research Chemicals. [g] B. p., 103–109°, obtained from Research Chemicals. [h] In a similar experiment 4 g. of catalyst was added to the reactants cooled to −70° and the temperature was then permitted to rise slowly. A sudden reaction occurred at −30°, the temperature reaching +30° in less than one minute; about one-third of the liquid was blown from the test-tube. Compounds VII (14 g.) and VIIA (10 g.) were obtained by distillation of the residue. [i] Autoclave rotated at room temperature for one hour, then at 40° for three hours.

TABLE II

PROPERTIES OF THE POLYCHLORO PRODUCTS

Compd.	Formula	B. p., °C.	Mm.	B. p. at 760 mm. °C.[a]	$n^{20}D$	d^{20}_4	Mol. ref. Calcd.	Obs.	Analyses,[b] %: Calcd. C	H	Cl	Found C	H	Cl
I	$(CH_3)_2CHCHClCHCl_2$[c]	66–67	16	173–174	1.4709		39.9		34.20	5.17	60.63	34.52	5.17	59.74
I[a]	$(CH_3)_2CHCHClCHCl_2$[c]	66–67	15	174–175	1.4705	1.2355	39.9	39.7	34.20	5.17	60.63	33.99	5.17	61.09
I[b]	$(CH_3)_2CHCHClCHCl_2$[c]	67–68	16	174–175	1.4710	1.2364	39.9	39.7	34.20	5.17	60.63	34.37	5.11	61.01
II	$(CH_3)_3CCHClCHCl_2$	60–60	4	199–199[d]	1.4770	1.2109	44.5	44.2	38.00	5.85	56.15	38.54	5.65	56.05
III	$(CH_3)_2CHCH_2CCl_2CH_2Cl$	56–58	6	185–187	1.4660	1.1793	44.5	44.5			56.15			56.62
IV	$(CH_3)_3CCH_2CCl_2CH_2Cl$[e]	54–54	2.5	202–202	1.4720	1.1631	49.1	49.0			52.27			53.07
V	$(CH_3)_3CCHClCCl_2CH_3$[e]	55–56	3	199–200[f]	1.4788	1.1682	49.1	49.3			52.27			51.55
VI	$C_{17}H_{13}Cl_3$[g]	62–67	4	201–207	1.4709									
VIA	$C_6H_8Cl_4$[h]	93–94	3.5	245–246	1.5100	1.3559	49.1	49.0			63.92			63.43
VII	$(CH_3)_2CHCHClCCl_3$	53–54	5	185–186	1.4860	1.3538	44.9	44.5	28.59	3.84	67.57	29.14	4.05	67.39
VIIA	$C_5H_7Cl_3$	45–46	15	152–153	1.4782	1.2436	39.6	39.5	34.60	4.07	61.33	34.62	4.14	61.47
VIII	$CH_2ClCHCl_2$[i]	111–112	745		1.4709									

[a] Calculated from boiling point under reduced pressure using nomograph prepared for hydrocarbon boiling-point conversions. This was found to give accurate results for halogenated hydrocarbons. [b] Microanalyses by Dr. T. S. Ma, University of Chicago. [c] The infrared spectra of I, Ia, and Ib showed that the compounds were identical. [d] M. p. −14 to −13°. [e] The infrared spectra of IV and V showed that the compounds were definitely different. [f] M. p. −38 to −37°. [g] Probably a mixture of 1,2,3-trichloro-4,4-dimethylpentane and 1,1-dichloro-2-chloromethyl-3,3-dimethyl butane. [h] This compound was also obtained by the action of aluminum chloride (3 g.) on 1,3-dichloro-1-propene (52 g.) at −10 to 0°. Yield was 4 g., b. p. 88–91° at 2.5 mm.; $n^{20}D$ 1.5123. [i] *Cf.* Beilstein, 4th ed. Vol. I, p. 85, and the corresponding page in the second supplement.

into solution. A 75% yield of the trichlorohexane was obtained.

Similar observations were made in other cases. It was often found that the addition of 1 g. of aluminum chloride to about 50–100 g. of reactants gave rather little reaction and that the addition of a second portion of catalyst to the resulting solution resulted in a vigorous reaction. In some cases, a small amount (1–5 g.) of catalyst complex "lower layer" separated.

Acknowledgments.—The author wishes to thank Dr. W. S. Gallaway of the Physics Division, Universal Oil Products Company, for the comparison of some of the chlorides by means of their infrared spectra and Mr. E. E. Meisinger for assistance in the experimental work. The continued interest and advice of Professor V. N. Ipatieff is also gratefully acknowledged.

Summary

1. Trichloroalkanes are formed by the reaction of alkyl chlorides (*e. g.*, *n-* and isopropyl and *t*-butyl chlorides) with dichloroölefins (*e. g.*, *cis-* and *trans*-dichloroethylene and the three dichloro-

propenes) in the presence of aluminum chloride.

2. There is a marked difference in reactivity between *cis*- and *trans*-dichloroethylene. The former may be condensed in good yield with isopropyl and *t*-butyl chlorides, whereas the latter gives only a fair yield of product with the propyl halide and a very poor yield with the butyl compound.

3. Ethyl chloride could not be condensed with *cis*-dichloroethylene.

4. The reaction of isopropyl chloride with trichloroethylene in the presence of aluminum chloride at 0–20° yields tetrachloropentane (presumably 1,1,1,2-tetrachloro-3-methylbutane) and its dehydrochlorination product, trichloropentene.

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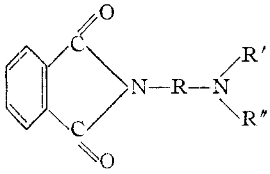
[CONTRIBUTION FROM THE ABBOTT LABORATORIES]

N-Alkamine Substituted Phthalimides[1]

BY M. B. MOORE AND R. T. RAPALA

For a number of years, one of us[1a] has been interested in the synthesis of N-alkamine substituted phthalimides useful as local anesthetics. Some compounds of this type have previously been synthesized[2] but no study of their pharmacologic action has been reported. In many cases they were not carefully purified, but were immediately hydrolyzed to the diamines according to the Gabriel method,[3] or a modification of this.

Table I lists the compounds prepared in this series conforming to the general formula



in which R is an alkylene group, straight or branched; R′ and R″ are alkyl groups or hydrogen or may complete a heterocyclic ring of which the nitrogen is a member. Other modifications which do not conform to the above general type will be reported later.

Experimental

The five methods used are illustrated by the following procedures:

N-γ-Diethylaminopropylphthalimide, Method A.—Phthalic anhydride (74 g., 0.5 mole) and γ-diethylaminopropylamine (65 g., 0.5 mole) were heated in an oil-bath at 160–180° for an hour. After cooling, the viscous liquid product was taken up in water with a slight excess of hydrochloric acid. The aqueous solution was filtered with a little Darco, and the oily base precipitated from the clear aqueous solution of the hydrochloride by addition of excess sodium carbonate. The base was shaken out in petroleum ether, and solvent evaporated. The base was then taken up in a little absolute alcohol, and the crystalline hydrochloride precipitated therefrom by addition of alcoholic hydrochloric acid, with ice cooling; dry ether was added to give more complete precipitation. After filtration and washing with ether, the air-dried crystals weighed 142 g. After drying in a vacuum at boiling acetone temperature with phosphorus pentoxide, the alcohol of crystallization was lost.

Method B.—Phthalimide (14.7 g., 0.1 mole) and γ-diethylaminoproylamine (13.0 g., 0.1 mole) were gently heated together in an oil-bath at 90–110° for four and one-half hours. During the first hour, evolution of ammonia occurred and the mixture became a viscous liquid. The product was taken up in aqueous hydrochloric acid and further purified as described under Method A.

N-β-Di-*n*-butylaminoethylphthalimide, Method C.—β-Di-*n*-butylaminoethyl chloride (19.5 g., 0.1 mole) and potassium phthalimide (19 g., 0.1 mole) were refluxed with 100 cc. of absolute alcohol (12A) for eleven hours. The reaction mixture was filtered from the precipitate of potassium chloride, and the alcohol distilled under vacuum from the filtrate. The residue was taken up in petroleum ether, solution filtered and distilled. The fraction, b. p. 161–177° (2.5 mm.), amounted to 11 g. It was further purified by solution in aqueous hydrochloric acid and filtration with charcoal, followed by liberation of the base and its extraction with ether.

N-ω-Diethylaminohexylphthalimide, Method D.—N-ω-Bromohexylphthalimide (7.8 g., 0.025 mole), diethylamine (7.3 g., 0.1 mole) and 50 cc. of absolute alcohol (12A) were refluxed for eleven hours. The solution was filtered and solvent distilled at atmospheric pressure. The residue was partitioned between water and petroleum ether to remove water-soluble impurities. The dried petroleum ether extracts were evaporated and the residue taken up in absolute alcohol and precipitated by hydrochloric acid, ether being added to aid in complete precipitation. The precipitate was recrystallized from a small volume of 12A absolute alcohol.

N-Morpholinomethylphthalimide, Method E.—Phthalimide (39.4 g., 0.2 mole) in a small round-bottomed flask was covered with dilute alcohol (1:1). The mixture was stirred, and 40 cc. formalin was added, followed by morpholine (17.5 g., 0.2 mole). With continued stirring, the magma was heated to refluxing and refluxed for fifteen minutes, after which nearly all was dissolved. The solution was filtered hot and, after three days in the cold room, the crystalline product was filtered and recrystallized from 3A alcohol.

The pharmacology of these compounds was studied by Dr. R. K. Richards and co-workers and will be reported in detail elsewhere. Most of the compounds possessed local anesthetic properties, γ-diethylaminopropylphthalimide being the best of the series for injection anesthesia from the standpoint of efficiency, toxicity and lack of irritation. Its properties in general are quite similar to those of procaine. Increase in the length of the alkylene chain beyond three carbons tends to increase toxicity without a cor-

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[1] Presented on the program of the Division of Medicinal Chemistry at the Atlantic City meeting of the American Chemical Society, April 8–12, 1946.

[1a] Moore, U. S. Patent 2,343,198 (1944).

[2] (a) Sachs, *Ber.*, **31**, 3230 (1898); (b) Walls, *J. Chem. Soc.*, 104 (1934); (c) Shriner and Hickey, THIS JOURNAL, **61**, 888 (1939); (d) Kharasch and Fuchs, *J. Org. Chem.*, **9**, 359 (1944).

[3] (a) Gabriel, *Ber.*, **20**, 2224–2236 (1887); (b) **21**, 566–575 (1888); (c) **22**, 2223–2227 (1889); and many later papers.