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Reduction of Carbonyl Groups by a Model for a Coenzyme[1]

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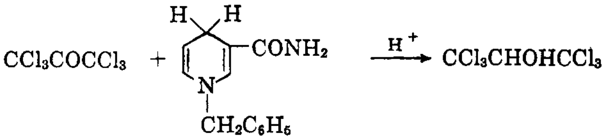
Hexachloroacetone in formamide is reduced to hexachloroisopropyl alcohol by 1-benzyl-1,4-dihydronicotinamide rapidly and in nearly quantitative yield at room temperature. Approximately 40% of the available deuterium is transferred to the carbonyl carbon from 1-benzyl-4-deuterio-1,4-dihydronicotinamide. When the reaction was carried out in cyclohexene in the presence of peroxide or under ultraviolet light, reduction occurred almost exclusively at the trichloromethyl group to yield pentachloroacetone, 1-benzyl-3-carbamoylpyridinium chloride, and a mixture of *sym*- and *unsym*-tetrachloroacetone. When the reaction was carried out in nitromethane, reduction occurred both at the carbonyl group and at the trichloromethyl group. In this solvent, free radical inhibitors completely suppressed the formation of pentachloroacetone, but had no effect on the yield of hexachloroisopropyl alcohol. Evidence for reduction of chloral, *sym*-tetrachloroacetone, and *sym*-difluorotetrachloroacetone was obtained.

The reduction of hexachloroacetone in good yield to hexachloroisopropyl alcohol by 1-benzyl-1,4-dihydronicotinamide, a "model" for the reduced coenzyme dihydronicotinamide–adenine dinucleotide (NADH),[4] is believed to be the first example of the efficient nonenzymic reduction of a ketone by a dihydronicotinamide.[5] The keto groups of pyruvic acid,[6] benzoylformic acid,[6c] benzil,[7] and alloxan[6a] have been reduced by derivatives of dihydropyridines in low or in unstated yields.[8] Quinones and related compounds are reduced nonenzymically by NADH or its models.[7a,9] Complexes of lithium aluminum hydride with pyridine, said to consist of a dihydropyridine complexed with aluminum, reduce electrophilic carbonyl groups such as that in hexachloroacetone readily.[10]

Thiobenzophenone and its substituted analogs are reduced readily and in good yield by 1-benzyl-1,4-dihydronicotinamide.[11] The olefinic double bond of 1-phenyl-4,4,4-trifluoro-2-butene-1-one was reduced rather than the carbonyl group by 1,2,6-trimethyl-3,5-dicarboethoxy-1,4-dihydropyridine.[12]

Results and Discussion

Reduction of Hexachloroacetone in Formamide.—The yields (53–60%) of hexachloroisopropyl alcohol reported in a preliminary note[5] were obtained by a heterogeneous reaction of equimolar quantities of hexachloroacetone and 1-benzyl-1,4-dihydronicotinamide in dry formamide. By the use of a 1-mole excess of ketone the yield of alcohol has been increased to 97% (based on 1-benzyl-1,4-dihydronicotinamide).



The decrease in yield obtained when equimolar portions of the reactants were used may be caused by a haloform cleavage of part of the ketone by residual water present in the formamide.[13] It was difficult to remove water from formamide. A blank run of purified formamide and hexachloroacetone gave a quantitative yield of chloroform and an acidic solution when done under the same conditions as a run in which the dihydronicotinamide was present. The hydrogen transfer apparently is competitive with the rapid hydration of hexachloroacetone.

$$CCl_3COCCl_3 + H_2O \longrightarrow CHCl_3 + CCl_3COOH$$

The solubility of hexachloroacetone in formamide is low, and the rate at which one phase is attained depends on the rate of stirring. Normally, one phase is observed after 5 to 10 min. at room temperature. In reactions in which 2 moles of ketone was used, 20 min. was required. In either case, analysis by gas chromatography at the end of the time required for a homogeneous solution to be formed showed the hexachloroacetone to be completely exhausted.

Free radical chain inhibitors, hydroquinone or *t*-butyl catechol, had no effect on the yield of alcohol nor did the presence of metal salts[14] (except copper salts). When cupric bromide or copper(II) α,α'-dipyridyl sulfate was present, the yield of alcohol was decreased and was accompanied by the formation of pentachloroacetone and tetrachloroacetone.

The reduction of cupric ion by 1-benzyl-1,4-dihydronicotinamide has been observed,[15] and it appears that cupric or cuprous ion catalyzes a free radical reaction of hexachloroacetone and the dihydro compound. This type of reaction will be discussed in a later section.

Hexachloroacetone also was reduced in good yield by 1-benzyl-3-acetyl-1,4-dihydropyridine which rules out any hydrogen transfer mechanism which involves a unique dependence on the carboxamide group.

About 40% of the available deuterium was transferred from 1-benzyl-4-deuterio-1,4-dihydronicotinamide to hexachloroacetone. Infrared and proton magnetic resonance spectroscopy showed that the deuterium was present at the secondary carbon of the carbinol. The deuterium present in the 4-position of the dihydro compound and in the 2-position of hexachloro-

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(2) Department of Chemistry, Syracuse University, Syracuse 10, N. Y.

(3) University Fellow, 1962–1963; Edgar Fahs Smith Scholar, 1961–1963.

(4) DPNH by an older nomenclature.

(5) D. C. Dittmer, L. J. Steffa, J. R. Potoski, and R. A. Fouty, *Tetrahedron Letters*, **No. 22**, 827 (1961).

(6) (a) D. Mauzerall and F. H. Westheimer, *J. Am. Chem. Soc.*, **77**, 2261 (1955); (b) K. Wallenfels, and D. Hofmann, *Tetrahedron Letters*, **No. 15**, 10 (1959); (c) R. Abeles and F. H. Westheimer, *J. Am. Chem. Soc.*, **80**, 5459 (1958).

(7) (a) E. A. Braude, J. Hannah, and R. Linstead, *J. Chem. Soc.*, 3257 (1960); (b) J. M. Kolyer, Ph.D. Thesis, University of Pennsylvania, 1960, p. 159.

(8) A review of models for enzymic hydrogen transfers is given by F. H. Westheimer, "The Enzymes," P. D. Boyer, H. Lardy, and K. Myrbäck, Ed., 2nd Ed., Vol. 1, Academic Press, Inc., New York, N. Y., 1959, p. 278.

(9) W. D. Wosilait and A. Nason, *J. Biol. Chem.*, **206**, 255 (1954); K. Wallenfels and M. Gellrich, *Ann.*, **621**, 149 (1959); H. Kühnis, W. Traber, and P. Karrer, *Helv. Chim. Acta*, **40**, 757 (1957).

(10) P. T. Lansbury and J. O. Peterson, *J. Am. Chem. Soc.*, **83**, 3537 (1961).

(11) R. H. Abeles, R. F. Hutton, and F. H. Westheimer, *ibid.*, **79**, 712 (1957).

(12) B. E. Norcross, P. E. Klinedinst, Jr., and F. H. Westheimer, *ibid.*, **84**, 797 (1962).

(13) E. G. Edwards, D. P. Evans, and H. B. Watson, *J. Chem. Soc.*, 1942 (1937).

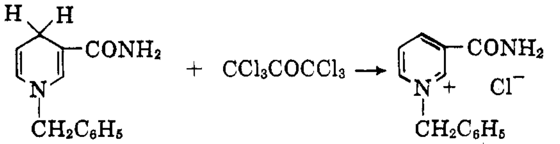
(14) Lithium chloride, barium chloride, zinc chloride, bis(ethylenediamine)cobalt(III) chloride, and zinc chloride–*o*-phenanthroline complex.

(15) D. C. Dittmer and J. M. Kolyer, *J. Org. Chem.*, **27**, 56 (1962); ref. 7b, p. 205.

isopropyl alcohol was nonexchangeable under the conditions of the reaction. Since the product carbinol has about 20% deuterium at the 2-carbon, it appears that an isotope effect of about 4 in favor of the light isotope is present.[16]

In formamide solvent the isolation of the quaternary pyridinium salt was not possible, although in the absence of solvent it could be obtained.[5] Hexachloroisopropyl alcohol could be obtained directly from the reaction mixture without addition of protons. Hexachloroisopropoxide ion may remove a proton from formamide or from residual water to yield an anion which destroys the pyridinium ring.[17]

Reactions in Cyclohexene.—When the reduction of hexachloroacetone was attempted by use of a suspension of 1-benzyl-1,4-dihydronicotinamide in cyclohexene[18] which had not been freshly purified, the temperature rose rapidly and the yellow suspension of 1-benzyl-1,4-dihydronicotinamide was replaced rapidly and quantitatively by a white suspension of 1-benzyl-3-carbamoylpyridinium chloride. Other products of the reaction were pentachloroacetone, a mixture of *sym*- and *unsym*-tetrachloroacetone, and water. No hexachloroisopropyl alcohol was found.



$$+ \ CCl_3COCHCl_2$$

$$+ \ CCl_3COCH_2Cl + CCl_2HCOCHCl_2 + H_2O$$

A similar reaction was obtained in carefully purified cyclohexene or in hexane to each of which had been added a few drops of *t*-butyl hydroperoxide. In the absence of any added peroxides in pure cyclohexene in the dark only small amounts of the above products were obtained and a low yield of hexachloroisopropyl alcohol was produced. A reaction mixture in pure cyclohexene when exposed for a given time to light or to ultraviolet radiation gave considerably more quaternary pyridinium salt than a reaction mixture in the dark. The yields of alcohol in these radiation-catalyzed reactions remained essentially constant. Photolysis of hexachloroacetone yields trichloromethyl radicals,[19] and these could initiate the radical chain reaction shown below.

The scheme to account for the peroxide-catalyzed reaction is analogous to one proposed by Kurz, Hutton, and Westheimer for the reduction of bromotrichloromethane.[20] The radicals **1** and **2** can abstract a hydrogen atom from the dihydropyridine ring to yield the two tetrachloroacetones. No dimers of the radicals were isolated, but they may have been present in small amounts.

$$RO\cdot + DH_2{}^{21} \longrightarrow DH\cdot + ROH$$

$$DH\cdot + CCl_3COCCl_3 \longrightarrow DHCl + \cdot CCl_2COCCl_3$$

$$DHCl \longrightarrow DH^+Cl^-$$

$$CCl_2COCCl_3 + DH_2 \longrightarrow CHCl_2COCCl_3 + DH\cdot$$

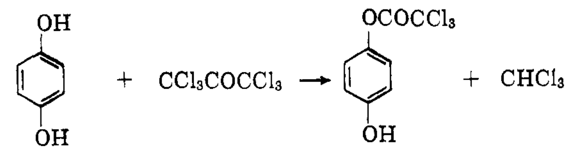
$$DH\cdot + CHCl_2COCCl_3 \longrightarrow \underset{\mathbf{1}}{CHCl_2COCCl_2\cdot} + \underset{\mathbf{2}}{\cdot CHClCOCCl_3}$$

Methyl iodide and 1-phenyl-1,4-dihydropyridine yield 1-phenylpyridinium iodide,[22] probably by a similar route. The radical **1** should be more stable than **2**,[23] and this difference in stabilities may account for the greater amount of symmetrical tetrachloroacetone produced. There are analogies for the removal of chlorine atoms from trichloromethyl groups.[19,24]

When 1-benzyl-4-deuterio-1,4-dihydronicotinamide was the reducing agent, partially deuterated pentachloroacetone was obtained in addition to a quantitative yield of partially deuterated 1-benzyl-3-carbamoylpyridinium chloride, a result in accord with the above reaction scheme.

Reactions in Nitromethane.—When the reduction of hexachloroacetone by 1-benzyl-1,4-dihydronicotinamide was carried out in nitromethane, in which both substrates were soluble, two types of hydrogen transfer occurred. When the reactants were mixed, heat was evolved and 1-benzyl-3-carbamoylpyridinium chloride (30–40%) precipitated within 2 min. Considerable hexachloroisopropyl alcohol (48–60%) was obtained on working up the reaction mixture. Analysis of the reaction mixture showed that the hexachloroacetone was completely gone after 2 min. Pentachloroacetone was present, but its concentration gradually decreased during the next hour.[25] The yield of alcohol was not appreciably changed when the reaction mixture was worked up after only 5 min., indicating that the reduction of the carbonyl group was fast. Similar results were obtained when 1-benzyl-3-acetyl-1,4-dihydropyridine was the reducing agent, but the reaction seemed slower, which may be related to the greater stability of the reduced 3-acetyl compound as compared with the 3-carbamoyl derivative of NAD.[26]

t-Butyl catechol completely suppressed the formation of 1-benzyl-3-carbamoylpyridinium chloride and pentachloroacetone, although the yield of hexachloroisopropyl alcohol was unchanged.[27] The formation of pentachloroacetone was inhibited also by hydroquinone, but the yield of alcohol was lowered because of a haloform-type cleavage of the ketone by the hydroquinone.



Yields of alcohol might have been expected to be higher in those runs in which the competing free-radical reaction is suppressed by inhibitors. This was not the case since both hydroquinone and *t*-butyl catechol decompose the ketone. *t*-Butyl catechol did not react

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[16] The experiments do not show whether all of the hydrogen obtained by the 2-carbon of hexachloroacetone in its conversion to hexachloroisopropanol comes from the dihydro compound so that the magnitude of the isotope effect is uncertain. An isotope effect of 4 to 5 was reported in the reduction of thiobenzophenone.[11]

[17] For a review of ring openings of pyridinium salts see H. S. Mosher, "Heterocyclic Compounds," R. C. Elderfield, Ed., Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 424.

[18] The cyclohexene was to trap any dichlorocarbene which might have been produced from the hexachloroacetone. [F. W. Grant and W. B. Cassie, *J. Org. Chem.*, **25**, 1433 (1960); P. K. Kadaba and J. O. Edwards, *J. Org. Chem.*, **25**, 1431 (1960).] No 7,7′-dichloronorcarane was found.

[19] S. Hautecloque, *Compt. rend.*, **254**, 3671 (1962).

[20] J. L. Kurz, R. Hutton, and F. H. Westheimer, *J. Am. Chem. Soc.*, **83**, 584 (1961).

[21] DH_2 = 1-benzyl-1,4-dihydronicotinamide; DHCl = 1-benzyl-4-chloro-1,4-dihydronicotinamide; DH^+Cl^- = 1-benzyl-3-carbamoylpyridinium chloride.

[22] M. Saunders and E. H. Gold, *J. Org. Chem.*, **27**, 1439 (1962).

[23] E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p. 744.

[24] A. N. Nesmeyanov, R. K. Friedlina, and L. I. Zakharin, *Quart Rev.* (London), **10**, 330 (1956).

[25] The disappearance of pentachloroacetone during the reaction may be caused by formation of tetrachloroacetone or pentachloroisopropyl alcohol, but no tetrachloroacetone could be detected by gas chromatography nor was there additional absorption in the hydroxyl stretching region in the infrared which could be attributed to pentachloroisopropyl alcohol.

[26] M. J. Spiegel and G. R. Drysdale, *J. Biol. Chem.*, **235**, 2498 (1960).

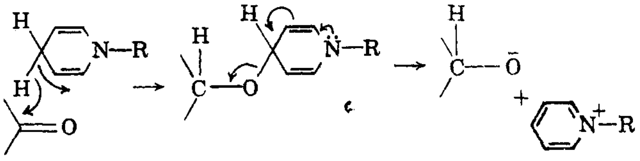
[27] All attempts to isolate the oxidized dihydronicotinamide derivative, which should be the only other product of the reduction, failed. Anions (alkoxide, hydroxide) in the reaction mixture may be destroying the pyridinium salt. Nitromethane is reported to form addition compounds with models for NAD [K. Wallenfels and H. Schüly, *Ann.*, **621**, 86 (1959)].

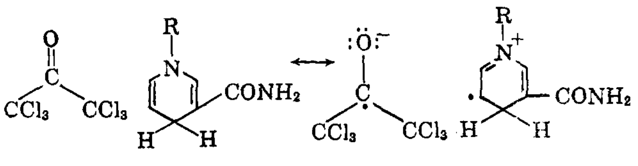
with hexachloroacetone in the absence of a basic catalyst, but in the presence of the dihydronicotinamide or collidine, chloroform formation was extensive.

Reductions of Other Carbonyl Compounds.—Chloral was reduced previously by 1-benzyl-1,4-dihydronicotinamide to trichloroethanol (3% yield)[5]; it is also reduced by 1-benzyl-3-acetyl-1,4-dihydropyridine in acetone (24 hr., room temperature) in 5% yield. Chloral is reported to be reduced in mammals to trichloroethanol.[28]

Both *sym*-tetrachloroacetone and *sym*-difluorotetrachloroacetone were treated with 1-benzyl-1,4-dihydronicotinamide in formamide. Infrared spectra of the oily product showed strong absorption in the hydroxyl stretching region which indicated reduction had occurred. It is unlikely that the hydroxyl absorption is caused by a ketone hydrate or cleavage product since when *sym*-difluorotetrachloroacetone in formamide was treated with dilute (3%) aqueous hydrochloric acid and then extracted continuously with hexane (in the same manner as the reaction mixtures containing the dihydronicotinamide were treated) no organic material was obtained when the hexane was evaporated.

Mode of Hydrogen Transfer.—The inhibition of the formation of pentachloroacetone and 1-benzyl-3-carbamoylpyridinium chloride by *t*-butyl catechol suggests strongly a free radical mechanism for the reaction yielding those products. The lack of effect of radical inhibitors on the formation of hexachloroisopropyl alcohol indicates that reduction of the carbonyl group is not by any free radical process which is capable of being stopped by these inhibitors. It is possible that the hydrogen is transferred to the carbonyl carbon as a hydrogen atom within a complex of ketone and dihydropyridine, the pyridine ring becoming attached to oxygen.[8] It is difficult to explain by such a mechanism why acetone or cyclobutanone[29] is not reduced, although preliminary complex formation could conceivably be facilitated by the electronegative ketone. The complex could be of the charge-transfer type[30] and can be represented as a hybrid of a number of resonance structures. Transfer of a hydrogen atom would complete the reaction.[31] Other complexes may involve addition of the carbonyl oxygen or carbonyl carbon to a carbon–carbon double bond of the dihydropyridine ring.[32]

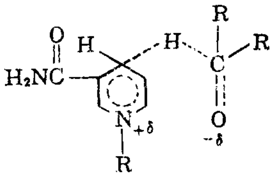




The hydrogen may be transferred also as a proton or hydride ion. A proton transfer to the electron-deficient carbonyl group in hexachloroacetone seems unlikely since such a transfer should occur more readily with acetone, which is not reduced. Direct proton transfer to the carbonyl oxygen would result in formation of a readily exchangeable proton which seems unlikely in view of the deuterium transfer experiments.

The ready reduction of the electron-deficient ketone is in agreement with the transfer of hydrogen as a hydride ion. Infrared stretching frequencies for the carbonyl groups in cyclobutanone, which is not reduced, and in hexachloroacetone, which is reduced, are nearly identical (1775 and 1780 cm.$^{-1}$, respectively). The reduction of hexachloroacetone is probably facilitated by the inductive and field effects of the trichloromethyl groups.

An attractive mechanism for reduction is similar to that proposed by Kosower[30b] for the oxidation of alcohols by NAD. The developing positive charge on the nitrogen in the transition state is attracted electrostatically to the developing negative charge on oxygen. The favorable effect of formamide as solvent may be due to hydrogen bonding or to electrostatic assistance in the polarization of the carbonyl group.



Experimental

All analyses by gas chromatography were carried out using a 2.5-m. column of 20% Silicone-550 on Chromosorb. The thermal conductivity cell was a Burrell Corp. Model SS detector, No. 340-148. Column temperature was controlled within ±2°.

All runs were carried out under a nitrogen atmosphere with the usual precautions being taken for the exclusion of moisture.

Hexachloroacetone (Eastman, Practical Grade) was purified by fractionation twice. The fraction boiling at 110° (40 mm.) gave a single peak when analyzed by gas chromatography. Formamide was purified by azeotropic removal of the water with benzene and fractionation of the residue at reduced pressure. The distillate was then dried over Molecular Sieves (Linde 4-A). Nitromethane (Matheson Coleman and Bell) was distilled from Drierite, b.p. 100° (atm.), and stored over Drierite until used. Cyclohexene (Matheson Coleman and Bell) was distilled from calcium hydride immediately before use.

Authentic hexachloroisopropyl alcohol, m.p. 86–87° (lit.[33] m.p. 86–87°), was prepared by the method of Geiger, Usteri, and Gränacher.[33] A proton magnetic resonance spectrum in carbon tetrachloride at 60 Mc. showed signals at 238 (O–H) (area 1.0) and 287 c.p.s. (C–H) (area 0.956) downfield from tetramethylsilane.

1-Benzyl-1,4-dihydronicotinamide was prepared according to the procedure of Mauzerall and Westheimer.[6a] Recrystallization from 44% ethanol gave long yellow needles, m.p. 118–120° (sintering at 115°) (lit.[6a] m.p. 120–122°). A proton magnetic resonance spectrum in chloroform-*d* at 60 Mc., tetramethylsilane as internal reference, was obtained. The assignment, relative area, and multiplicity, respectively, are given in parentheses. 186 (4-proton, 2.01, 2), 254 (methylene, 1.93, 1), 283 (5-proton, 1.0, 6), 341 (6-proton, 1.09, 2), 366 (NH_2, 2.0, 1), 426 (2-proton, 0.93, 1), and 436 c.p.s. (C_6H_5, 5.02, 1). The n.m.r. spectrum in chloroform-*d* with cyclohexane as an external reference has been published previously.[34]

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(28) von Mering, *Z. physiol. Chem., Hoppe-Seyler's*, **6**, 480 (1882).

(29) Cyclobutanone undergoes a ring-opening reaction with 1-benzyl-1,4-dihydronicotinamide in the presence of oxygen, but no reduction of the carbonyl group was observed. Details of this reaction will be reported in a subsequent paper.

(30) (a) R. S. Mulliken, *J. Phys. Chem.*, **56**, 801 (1952); (b) E. M. Kosower, *J. Am. Chem. Soc.*, **78**, 3497 (1956).

(31) It should be pointed out that a radical containing a trichloromethyl group adjacent to the site of the odd electron may undergo chlorine atom rearrangements [ref. 24; W. H. Urry and J. R. Eiszner, *J. Am. Chem. Soc.*, **74**, 5822 (1952)]. Such a rearrangement could lead to pentachloroacetone which was not observed in reactions in which radical inhibitors were present, although carbinol formation was not inhibited. This argues against any intermediate radical with an α-trichloromethyl group, but the argument is not pertinent to a charge-transfer complex which is represented by resonance structures formally like the above-mentioned intermediate but which are only conveniences and not realities. However, it is possible that a chlorine atom rearrangement could occur in a charge-transfer complex if the carbon α to the trichloromethyl group had considerable radical character.

(32) Additions of nucleophilic and electrophilic reagents to a carbon–carbon double bond in dihydropyridines have been reported or suggested: K. Wallenfels and D. Hofmann, *Tetrahedron Letters*, 151 (1962); A. Stock, E. Sann, and G. Pfleiderer, *Ann.*, **647**, 188 (1961); H. R. Mahler and J. Douglas, *J. Am. Chem. Soc.*, **79**, 1159 (1957).

(33) M. Geiger, E. Usteri, and C. Gränacher, *Helv. Chim. Acta*, **34**, 1335 (1951).

(34) W. L. Meyer, H. R. Mahler, and R. H. Baker, Jr., *Biochem. Biophys. Acta*, **64**, 353 (1962).

1-Benzyl-4-deuterio-1,4-dihydronicotinamide.—1-Benzyl-3-carbamoylpyridinium chloride (5.0 g., 0.020 mole) was added during 5 min. to a vigorously stirred solution of sodium carbonate (dried at 110° for 24 hr., 6.9 g.) and sodium dithionite (90% pure, 12.0 g., 0.052 mole) in 50 ml. of deuterium oxide (99.6%) at 45–47°. Precautions were taken for the exclusion of moisture.

The yellow solid which precipitated was filtered and partially dried on a Büchner funnel. This solid was heated with 100 ml. of refluxing ethanol and filtered. The filtrate was concentrated to a volume of 50 ml.; it was heated to reflux, 60 ml. of water was added, and the solution was allowed to cool to room temperature. Filtration gave 2.5 g. (43%) of product, m.p. 118–120° (lit.[6a] m.p. 120–122°). Concentration of the ethanol filtrate gave 0.9 g. of impure product, m.p. 112–120°. The total crude yield was 79%. A proton magnetic resonance spectrum in chloroform-*d* was taken. The observed signals, assignment, relative area, and multiplicity were: 186 (4-proton, 1.0, ?), 255 (methylene, 1.9, 1), 282 (5-proton, 1.06, 4), 344 (6-proton, 1.06, 2), 362 (NH_2, 1.9, 1), 428 (2-proton, 1.06, 1), and 437 c.p.s. (C_6H_5, 4.9, 1) (tetramethylsilane reference).

3-Acetyl-1-benzyl-1,4-dihydropyridine.—3-Acetyl-1-benzylpyridinium chloride (5.0 g., 0.02 mole) was added during 3 min. to a solution of sodium carbonate monohydrate (7.5 g.) and sodium dithionite (13.0 g., 90% pure) in 100 ml. of water at 45–47°. The yellow mixture was stirred at 45–47° for 10 min. and at room temperature for an additional 50 min. The mixture was extracted with five 300-ml. portions of petroleum ether (b.p. 30–60°) and the combined extracts were dried over anhydrous magnesium sulfate. The petroleum ether solution was concentrated to 100 ml. on a rotary evaporator during which time a yellow solid (2.3 g., 53%, m.p. 60–64°) precipitated. This solid was purified by stirring with 1 l. of petroleum ether and by concentration at room temperature as before. The product crystallized as pale yellow leaflets, m.p. 64–66° (lit.[35] m.p. 61–67°).

2-Deuteriohexachloroisopropyl alcohol was prepared by the reduction of hexachloroacetone with lithium aluminum deuteride according to the procedure utilized by Geiger, Usteri, and Gränacher for the preparation of hexachloroisopropyl alcohol.[33] There was obtained 18.4 g. (91%) of white 2-deuteriohexachloroisopropyl alcohol, m.p. 82–85°. Two crystallizations from hexane gave long flat needles, m.p. 86.5–87.5°. Intense infrared bands in carbon tetrachloride occurred at 3590, 3540, 1297, 1233, 1219, 943, 930, 842, 820, 710, and 588 cm.$^{-1}$. A proton magnetic resonance spectrum (60 Mc.) in carbon tetrachloride showed a single peak at 240 c.p.s. (tetramethylsilane reference). When 1 drop of acetic acid was added to the sample, the peak was broadened and was observed at 282 c.p.s.

Reduction of Hexachloroacetone in Formamide.—1-Benzyl-1,4-dihydronicotinamide (0.80 g., 0.0037 mole) was dissolved in 25 ml. of formamide in a 50-ml., three-necked flask equipped with a stirrer, reflux condenser, and gas inlet. Nitrogen was passed over the solution during the reaction. Hexachloroacetone (1.0 g., 0.0037 mole) was added in one portion, producing two layers. The mixture was stirred vigorously and one phase was attained after 10 min. The solution was stirred for 2 hr. at room temperature before 10 ml. of 3% hydrochloric acid was added. The resulting solution was extracted with hexane in a continuous extractor for 1 day. The hexane layer was separated and concentrated under vacuum on a rotary evaporator. A 57% yield of crude hexachloroisopropyl alcohol, m.p. 80–84°, was obtained. This solid was sublimed under reduced pressure to give long white needles, m.p. 85–87° (48%) (lit.[33] m.p. 86–87°). An infrared spectrum was identical with that of authentic hexachloroisopropyl alcohol.

When 1-benzyl-1,4-dihydronicotinamide (0.40 g., 0.0019 mole) and hexachloroacetone (0.50 g., 0.0019 mole) were stirred for 10 min. in 15 ml. of purified formamide, gas chromatography of the mixture showed the presence of chloroform in a quantity equivalent to 30% of the hexachloroacetone initially present. The hexachloroacetone was completely gone after 10 min. A 60% yield of hexachloroisopropyl alcohol was obtained.

In another run in the absence of solvent, the product was purified by chromatography on alumina (Woelm, Activity Grade 1). Flat plates, m.p. 85–87°, were obtained. A mixture melting point with authentic hexachloroisopropyl alcohol (m.p. 86–87°) was not depressed.

Anal. Calcd. for $C_3H_2OCl_6$: C, 13.50; H, 0.76; Cl, 79.75. Found: C, 13.48; H, 0.92; Cl, 79.86.

In another run using two equivalents of ketone per equivalent of reducing agent, a crude yield of 97% hexachloroisopropyl alcohol was obtained.

In the reduction of hexachloroacetone by 3-acetyl-1-benzyl-1,4-dihydropyridine, the ketone (1.0 g., 0.0037 mole) and dihydro compound (0.80 g., 0.0037 mole) were added to 25 ml. of purified formamide and the reaction mixture was stirred for 2 hr. The color changed from yellow to reddish brown within 15 min. The dark solution was hydrolyzed with 15 ml. of 3% hydrochloric acid and the resulting solution was extracted with hexane for 18 hr. The hexane was concentrated on a rotary evaporator, leaving 0.70 g. of pale yellow solid, m.p. 78–83°. The solid was sublimed to give 0.63 g. (63%) of long white needles, m.p. 86–87°. An infrared spectrum of this material was identical with that of authentic hexachloroisopropyl alcohol.

When the reducing agent was 1-benzyl-4-deuterio-1,4-dihydronicotinamide, a 54% yield of alcohol, m.p. 84–87°, was obtained. An infrared spectrum of a concentrated solution in potassium bromide showed absorption bands at 2923, 2226 (very weak), 2118 (very weak), 1380, 1336, 1271, 1103, 948, 924, 810 (broad), 718, 702, and 605 cm.$^{-1}$. A proton magnetic resonance spectrum of the product in carbon tetrachloride showed signals at 238 (O–H) (area 1.0) and 287 c.p.s. (C–H) (area 0.756) (tetramethylsilane reference). Deuterium was shown to be present at the secondary carbon of hexachloroisopropyl alcohol by comparison of the infrared spectrum of the product with those of the authentic carbinol and of authentic deuterated carbinol. The three spectra have identical absorption at 3537 and 3587 cm.$^{-1}$ in the hydroxyl-stretching region. In KBr, hexachloroisopropyl alcohol shows absorption for C–H stretching at 2923 cm.$^{-1}$. This band is absent in the spectrum of 2-deuteriohexachloroisopropyl alcohol, but a sharp new band appears at 2226 cm.$^{-1}$ which is presumably caused by a C–D stretching vibration. The spectrum of the carbinol product obtained by reduction of hexachloroacetone with 1-benzyl-4-deuterio-1,4-dihydronicotinamide shows a band of medium intensity at 2923 cm.$^{-1}$ and a weak band at 2226 cm.$^{-1}$.

The n.m.r. spectra of the three carbinols confirmed the results obtained by infrared spectra and also provided a way of estimating the deuterium content of the partially deuterated hexachloroisopropyl alcohol obtained in the reaction. The area of the signal of the proton on the secondary carbon of the partially deuterated carbinol relative to the area of the signal of the hydroxyl proton was 20% less than that of the undeuterated hexachloroisopropyl alcohol.

Reduction of Hexachloroacetone in Cyclohexene.—Hexachloroacetone (1.0 g., 0.0037 mole) and 1-benzyl-1,4-dihydronicotinamide (0.80 g., 0.0037 mole) were mixed in 15 ml. of purified cyclohexene containing 5 drops of *t*-butyl hydroperoxide. The dihydro compound was insoluble and the mixture was stirred vigorously for 2 hr. during which it gradually became tan. Filtration gave 0.91 g. (98%) of 1-benzyl-3-carbamoylpyridinium chloride, m.p. 228–234° dec. A mixture melting point with authentic salt was not depressed. An infrared spectrum was identical with that of authentic 1-benzyl-3-carbamoyl-pyridinium chloride. Similar results were obtained in reaction in impure cyclohexene in the absence of added peroxide.

Anal. Calcd. for $C_{13}H_{13}ON_2Cl$: C, 62.78; H, 5.27; N, 11.27; Cl, 14.26. Found: C, 62.50; H, 5.06; N, 11.19; Cl, 14.35.

The cyclohexene filtrate was concentrated on a rotary evaporator, leaving 0.7 g. of a light yellow liquid residue which was analyzed by gas chromatography at 180° and a helium flow of 55 ml./min. Other than cyclohexene, three peaks appeared at retention times of 5.7, 7.4, and 11.1 min. The relative areas of these peaks were in the ratio of 16:68:16. Samples of each of these components were obtained by collection of samples of the eluent from the column. The component appearing at 11.1 min. was identified as hexachloroacetone by comparison of its infrared spectrum with that of an authentic sample. The components appearing at 7.4 and 5.7 min. were identified as pentachloroacetone and a mixture of *sym*- and *unsym*-tetrachloroacetone,[36] respectively, by mass spectrometry.

In several reactions of the above type, the residue (after almost complete removal of the cyclohexene) was completely volatile and accounted for 85–95% of that weight expected after one equivalent of chlorine is removed from hexachloroacetone, indicating that most of the salt formation is accounted for by the formation of penta- and tetrachloroacetone.

Table I summarizes some results obtained under various reaction conditions.

1-Benzyl-4-deuterio-1,4-dihydronicotinamide (0.40 g., 0.0019 mole) and hexachloroacetone (0.50 g., 0.0019 mole) were mixed in 100 ml. of purified cyclohexene containing 4 drops of *t*-butyl hydroperoxide. After 2 hr., 0.44 g. (95%) of 1-benzyl-3-carbamoylpyridinium chloride was removed by filtration. Concentration of the filtrate left 0.45 g. of pale yellow residue which was analyzed by gas chromatography at 183° and a helium flow of 75 ml./min. Three peaks appeared at retention times of 5.0, 6.4, and 9.9 min. The relative areas of these peaks were in the ratio of 26:54:20. The material whose retention time was 6.4 min. was collected. Its infrared spectrum was superimposable with that of authentic pentachloroacetone with the exception of two weak bands at 1145 and 943 cm.$^{-1}$ and a band of medium intensity at 908 cm.$^{-1}$. These bands may be caused by carbon–deu-

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(35) A. G. Anderson, Jr., and G. Berkelhammer, *J. Am. Chem. Soc.*, **80**, 992 (1958).

(36) The fragment corresponding to $CHCl_2$ was more abundant than the fragment corresponding to CH_2Cl which may indicate that the *sym*-tetrachloroacetone was the major tetrachloro species.

TABLE I

REACTIONS OF 1-BENZYL-1,4-DIHYDRONICOTINAMIDE AND HEXACHLOROACETONE IN PURIFIED CYCLOHEXENE

Conditions	Alcohol, %	Tar, g.	Salt, %	Ratio of products H[a]	P[a]	T[a]
4 hr., dark	8	0.80[b]	5	88	12	..
12 hr., dark	38	.60	48	..	..	..
4 hr., light	9	.88[b]	26	68	26	6
3 hr., ultraviolet	7	.55	67	20	65	15
4 hr., *t*-BuO_2H	0	0	95–100	16	68	16
4 hr., *t*-BuO_2H[c]	0	0	0	100	0	0

[a] H = hexachloroacetone; P = pentachloroacetone; T = tetrachloroacetone. Ratios are relative areas of peaks obtained by gas chromatography. [b] Includes recovered dihydro compound. [c] 1-Benzyl-1,4-dihydronicotinamide omitted.

terium bending vibrations. Infrared absorption at 1205 and 1278 cm.$^{-1}$ is found in pentachloroacetone and at 1200 and 1280 cm.$^{-1}$ in tetrachloroacetone; these absorptions are not found in hexachloroacetone and are probably caused by carbon–hydrogen bending vibrations. These same vibrations involving a carbon–deuterium bond instead of a carbon–hydrogen bond might be expected to cause absorption in the 850–950 cm.$^{-1}$ region.[37] The bands at 1205 and 1278 cm.$^{-1}$ in the partially deuterated compound appear less intense relative to the absorption caused by the carbonyl group than do the bands in the undeuterated material. The C–H stretching frequency at 3018 cm.$^{-1}$ also is less intense in the partially deuterated pentachloroacetone. No C–D stretching absorption was observed.

Reduction of Hexachloroacetone in Nitromethane. 1. In the Absence of Inhibitors.—1-Benzyl-1,4-dihydronicotinamide (0.80 g., 0.0037 mole) was dissolved in 20 ml. of nitromethane and a solution of 1.0 g. (0.0037 mole) of hexachloroacetone in 5 ml. of nitromethane was added in one portion. The vigorously stirred solution became light brown and was analyzed immediately by gas chromatography at 182° and a helium flow of 70 ml./min. A peak appeared at 5.9 min. and was not resolved from a peak which appeared to have a maximum of 5.1 min. No peak due to hexachloroacetone was present. The analysis was repeated after 20, 35, and 60 min. In each analysis the peak at 5.9 min. was smaller than previously while the shoulder at 5.1 was not affected. No further decrease was noted when the reaction mixture was analyzed after 2 hr. The area of the peak at 5.9 min. was increased by the addition of a small sample of pentachloroacetone to the residue and analysis as before.

A salt was observed to precipitate within 2 min. after mixing the reactants and the temperature rose from 25 to 35°. 1-Benzyl-3-carbamoylpyridinium chloride (40%) was filtered from the reaction mixture after 2 hr. The filtrate was hydrolyzed with 15 ml. of 3% hydrochloric acid and extracted with hexane for 2 days. Concentration of the hexane left 0.80 g. of a mushy solid. An infrared spectrum showed a doublet in the 1750–1770 cm.$^{-1}$ region in addition to bands due to hexachloroisopropyl alcohol. This solid was sublimed to give 0.48 g. (48%) of hexachloroisopropyl alcohol, m.p. 84–86°.

Anal. Calcd. for $C_3H_2OCl_6$: C, 13.50; H, 0.76; Cl, 79.75. Found: C, 13.76; H, 1.00; Cl, 79.50.

In another run in which two equivalents of ketone per equivalent of reducing agent was used, the mushy solid obtained was analyzed by gas chromatography at 150° and a helium flow of 70 ml./min. A peak which appeared at 10.9 min. was collected and its infrared spectrum was found to be identical with that of an authentic sample of pentachloroacetone. A small peak believed due to tetrachloroacetone was not identified.

2. In the Presence of *t*-Butyl Catechol.—The reaction was repeated in the presence of 0.3 g. of *t*-butyl catechol. When the reagents were mixed, no immediate brown coloration was noted and the reaction was not exothermic. Analysis of the solution by gas chromatography after 2 hr. showed only traces of pentachloroacetone. No salt precipitated. After 1 hr. the solution was worked up as before to give 0.9 g. of off-white solid. An infrared spectrum of the solid showed no bands in the carbonyl region. The solid was chromatographed on neutral alumina to give a 50% yield of hexachloroisopropyl alcohol.

3. In the Presence of Hydroquinone.—Hexachloroacetone (1.0 g., 0.0037 mole) was dissolved in 10 ml. of nitromethane and the resulting solution was added dropwise during 35 min. to a solution of the dihydro compound (0.80 g., 0.0037 mole) and hydroquinone (0.3 g.) in 20 ml. of nitromethane during 40 min. No salt precipitated and the reaction mixture was worked up as before to give 0.58 g. of white solid, m.p. 55–67°. This solid was dissolved in a minimum of hot hexane and the solution was allowed to cool to room temperature. Filtration gave 0.2 g. of white needles, m.p. 86–86.5°. A mixture melting point with hexachloroisopropyl alcohol (m.p. 86–87°) was 57–78°. Infrared bands (in KBr) occurred at 3500 (free O—H), 3420, (bonded O—H), 1761 (C=O, halogenated ester), 1593 (aromatic), 1498 (aromatic), 1446, 1360 (O—H deformation), 1216 (C—O stretch, ester), 1114 (C—O stretch, phenol), 1093 (1,4-substitution), 1006 (1,4-substitution), 966, 870, 834 (1,4-substitution), 817, 785, and 674 cm.$^{-1}$ (C—Cl).

Anal. Calcd. for $C_8H_5O_3Cl_3$ (*p*-hydroxyphenyl trichloroacetate): C, 37.61; H, 1.97; Cl, 41.63. Found: C, 37.77; H, 2.12; Cl, 41.77.

This same product was obtained in 65% yield by the reaction of hexachloroacetone and hydroquinone in nitromethane in the presence of collidine. Hydrolysis with 10% hydrochloric acid gave hydroquinone and presumably trichloroacetic acid. The hydroquinone was identified by its melting point, infrared spectrum, and mixture melting point with an authentic sample.

Reduction of Chloral.—Chloral (0.553 g., 0.00375 mole) and 1-benzyl-3-acetyl-1,4-dihydropyridine (0.80 g., 0.0037 mole) were mixed in 19 ml. of acetone and the solution was stirred under nitrogen at 25° for 23 hr. The dark solution was then analyzed by gas chromatography on a column of 15% Carbowax 20,000 on Fluoropak-80 at 213° and a helium flow of 60 ml./min. Other than acetone and chloral, two peaks appeared at retention times of 8.4 and 12.5 min. The peak of 12.5 min. was isolated and its infrared spectrum was identical with that of authentic trichloroethanol. Calculations indicated that about a 5% yield of trichloroethanol had formed.

The peak at 8.4 min. was twice the area of the peak due to trichloroethanol. This component has not been identified.

Reduction of Tetrachloroacetone.—*sym*-Tetrachloroacetone (0.37 g., 0.0019 mole), prepared by the method of Zincke and Kegel,[38] was mixed with 1-benzyl-1,4-dihydronicotinamide (0.40 g., 0.0019 mole) in 15 ml. of formamide. The mixture was stirred for 2 hr.; 7 ml. of 3% hydrochloric acid was added, followed by extraction with hexane for 1 day. The hexane was concentrated to yield 0.12 g. of a light brown oil. Infrared bands in carbon tetrachloride solution occurred at 3598, 3554, 2958, 1752 (weak), 1252, 1090, and 1005 cm.$^{-1}$.

Reduction of *sym*-Difluorotetrachloroacetone.—Difluorotetrachloroacetone (1.75 g., 0.0075 mole) and 1-benzyl-1,4-dihydronicotinamide (1.6 g., 0.0075 mole) were mixed in 35 ml. of formamide, and the mixture was stirred for 2 hr. Hydrochloric acid (15 ml., 3%) was added and the mixture extracted with hexane for 20 hr. The hexane layer was concentrated to 0.45 g. of residue. Infrared bands of the residue dissolved in carbon tetrachloride occurred at 3690, 3000, 1765, 1715, 1415, 1375, 1265, 1150–1025, 946, and 905–880 cm.$^{-1}$.

Distillation at reduced pressure resulted in decomposition of the residue. The product was not identified, but reduction of the carbonyl group was believed to have occurred since the infrared spectrum of the product had strong absorption in the hydroxyl stretching region. The carbonyl absorption in the product was weak, but it was strong in *sym*-difluorotetrachloroacetone.

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(37) R. N. Jones and C. Sandorfy, "Techniques of Organic Chemistry," A. Weissberger, Ed., Vol. IX, Interscience Publishers, Inc., New York, N. Y., 1956, p. 407.

(38) T. Zincke and O. Kegel, *Ber.*, **22**, 1478 (1889).