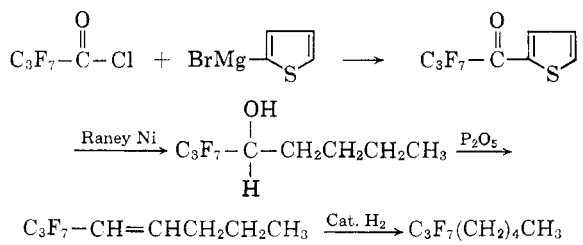
compounds and thus provide a method for preparation of heat-stable fluids. As described previously,[2] the preparation of 2-heptafluorobutyrylthiophene was achieved by a reverse Grignard technique. The attempted condensation of heptafluorobutyric acid and thiophene in the presence of phosphorus pentoxide, resulted only in the conversion of the fluorinated acid to the acid anhydride. Other methods were equally unsuccessful.

Reduction of 2-heptafluorobutyrylthiophene was unsuccessful *via* a Clemmensen or a Wolff-Kishner reaction using in the latter either 85% hydrazine hydrate or semicarbazide hydrochloride. Reductive desulfurization with Raney nickel resulted in the isolation of the alcohol 1,1,1,2,2,3,3-heptafluoro-4-octanol. The partially fluorinated olefin and hydrocarbon were then prepared as shown by the following over-all scheme.



In the reductive desulfurization reaction, a small amount of 1,1,1,2,2,3,3-heptafluoro-4-octanone was also isolated. Attempted reduction of this ketone by the Clemmensen or Wolff-Kishner reactions was unsuccessful. However, the ketone was easily converted in high yield to the alcohol by treatment with lithium aluminum hydride.

Experimental[3]

2-Heptafluorobutyrylthiophene.—An ether solution of 1 mole of thiophene magnesium bromide was added slowly to an ether solution of 1.2 moles of heptafluorobutyryl chloride and worked up in a manner previously described.[2] Distillation gave a 32% yield, b.p. 91.5–92.1° at 32 mm., $n^{20}D$ 1.43186.

Anal. Calcd. for $C_8H_3OF_7S$: C, 34.29; H, 1.08; F, 47.47. Found: C, 34.13; H, 1.25; F, 46.85.

The 2,4-dinitrophenylhydrazone, recrystallized from an alcohol–water mixture, melted at 90.2–90.8°.

1,1,1,2,2,3,3-Heptafluoro-4-octanol.—2-Heptafluorobutyrylthiophene (25 g., 0.09 mole), 250 g. Raney nickel,[4] and 900 ml. of 95% alcohol were stirred and refluxed for 16 hr. The alcohol was decanted and the nickel was washed with alcohol and ether. The solvents were distilled off, the remaining liquid dried overnight over anhydrous sodium sulfate and filtered. Fractionation gave 1,1,1,2,2,3,3-heptafluoro-4-octanol (9.5 g., 41%), b.p. 148.1–148.6°, $n^{25}D$ 1.34445.

Anal. Calcd. for $C_8H_{11}OF_7$: C, 37.51; H, 4.33; F, 51.92. Found: C, 38.31; H, 4.64; F, 52.65.

There was also isolated a small amount of 1,1,1,2,2,3,3-heptafluoro-4-octanone (1.0 g., 4%), b.p. 119.7–121.3°, $n^{25}D$ 1.326, semicarbazone 92.4–95.3°. These values correspond to that found in the literature.[5]

1,1,1,2,2,3,3-Heptafluoro-4-octene.—Phosphorus pentoxide (56.8 g., 0.4 mole) was placed in a 500-ml. flask and to this was added 1,1,1,2,2,3,3-heptafluoro-4-octanol (102.5 g., 0.4 mole). The mixture was distilled and the material from 59–124° collected. The distillate was washed with 5% sodium bicarbonate until slightly alkaline and then washed twice with distilled water. The combined washings were extracted once with ether. The ether-distillate solution was dried overnight over anhydrous sodium sulfate, filtered, and stripped of solvent. Fractionation through a 3-in. column with 1/8-in. helices gave 1,1,1,2,2,3,3-heptafluoro-4-octene (25.4 g., 27%), b.p. 105.3–106.2°, $n^{25}D$ 1.32980. Infrared spectra (max. at 5.98 μ) confirmed the olefin.

Anal. Calcd. for $C_8H_9F_7$: C, 40.34; H, 3.81; F, 55.85. Found: C, 40.52; H, 3.86; F, 55.39.

1,1,1,2,2,3,3-Heptafluoroöctane.—In a Parr hydrogenation apparatus was placed 1,1,1,2,2,3,3-heptafluoro-4-octene (16.8 g., 0.7 mole), 60 ml. of dry ether, and 90 mg. of platinum oxide catalyst.[6] After 26 hr. of hydrogenation, the solution was filtered, stripped of ether, and fractionated through a 3-in. column containing 1/8-in. helices. This gave 1,1,1,2,2,3,3-heptafluoro öctane (13.3 g., 79%), b.p. 108.8–109.6° at 751 mm., $n^{25}D$ 1.3226. Infrared spectra showed the absence of the double bond.

Anal. Calcd. for $C_8H_{11}F_7$: C, 40.01; H, 4.62; F, 55.38. Found: C, 40.48; H, 4.63; F, 55.41.

(2) S. Portnoy and H. Gisser, *J. Org. Chem.*, **22**, 1752 (1957).

(3) All temperature readings are uncorrected. The analyses were carried out by Wyanel Laboratories, Philadelphia, Pa. and by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(4) R. Mozingo, "Organic Synthesis," Coll. Vol. III, E. C. Horning ed., J. Wiley and Sons, Inc., New York, 1955, p. 181.

(5) K. T. Dishart and R. Levine, *J. Am. Chem. Soc.*, **78**, 2268 (1956).

(6) R. Adams, V. Voorhees, and R. L. Shriner, "Organic Synthesis," Coll. Vol. I, H. Gilman, ed., J. Wiley and Sons, Inc., New York, 1941, p. 463.

Potential Inhibitors of Cancerous Growth. I. Synthesis of Cyclic Nitrogen Mustard Phosphamide Ester Derivatives of D-Ribose

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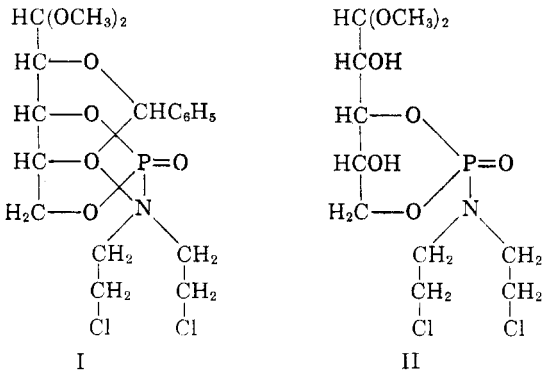
March 12, 1962

Arnold and co-workers[1] have shown that certain cyclic amide esters of phosphorylated nitrogen mustard have outstanding properties as anticancer agents. As a result compound IV (Cytoxan) has found successful clinical application in the treatment of certain cancers in various countries. It has been claimed[2] that IV acts as an inactive "transport form" which is reactivated in cancerous tissue by enzymic cleavage and removal of the electron-attracting phosphate group, thereby liberating free nitrogen mustard *in situ*. The same authors have also shown that a three carbon unit particularly as an aminopropane group as in (IV) in the heterocyclic ring system greatly enhances the clinical usefulness of the compounds.

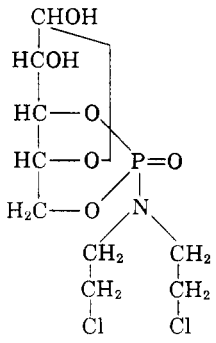
(1) H. Arnold, F. Bourseaux, and N. Brock, *Arzneimittel-Forsch.*, **11**, 143 (1961).

(2) H. Arnold and F. Bourseaux, *Angew. Chem.*, **70**, 539 (1958).

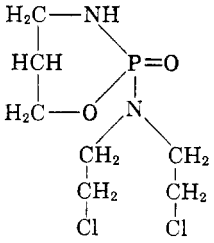


I

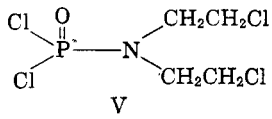
II



III



IV



V

This work, and in particular the importance attached to the composition of the heterocyclic ring system, suggested to us that the replacement of the aminopropane unit in IV by a substituted propane derivative, which plays a role in nucleic acid synthesis, might lead to a new type of "transport form" alkylating agent which could be expected to be reactivated at the site of nucleic acid synthesis in the cells. The 3,5-cyclophosphamide derivative (III) of D-ribose might be expected to conform to these requirements in view of the well known biological significance of ribose and its 3,5-cyclophosphate derivatives.[3]

Arnold and co-workers[1] have shown that the diester monoamide analogs of Cytoxan, which is a monoester diphosphamidate, are comparatively stable and therefore less suitable as "transport forms." Compound III, which strictly belongs to the latter type, differs from the series of compounds studied by these authors in that it contains a biologically significant structural unit.

The 2,4-*O*-benzylidene-D-ribose dimethyl acetal recently described by Potgieter and Mac Donald[4] was chosen as a starting material in the synthesis. Both hydroxyl groups in this compound reacted smoothly at room temperature with granular sodium in anhydrous dioxane. The resulting alkoxide liberated two equivalents of sodium hydroxide when dissolved in water and also reacted smoothly with bis(β-chloroethyl)phosphamido dichloride[5] (V) in anhydrous dioxane medium at room temperature, the calculated quantity of sodium chloride being precipitated. Product I was isolated from the reaction mixture as a light yellow oil which could not be crystallized.

Paper chromatography of the product in butanol–water showed one spot (R_f = 0.9), which could be revealed on paper after acid hydrolysis by spraying either with aniline phthalate (for the pentose unit), or with 4-(*p*-nitrobenzyl)pyridine (for the alkylating function),[6] or with ammonium molybdate–perchloric acid reagent (for phosphorus) confirming the presence of all these groupings in the molecule. Traces of free nitrogen mustard were also present on paper chromatograms.

Product I showed the typical chemical behavior of a "transport-form" nitrogen mustard derivative. Prior to acid hydrolysis of the compound, only slight alkylating properties could be detected using the quantitative procedure of Friedman and Boger[6] for the estimation of alkylating agents. Upon acid hydrolysis, the calculated amount of nitrogen mustard per molecule of I was liberated.

Removal of the benzylidene group in I was effected by catalytic hydrogenation in absolute methanol in the presence of palladized charcoal. Preliminary experiments showed that the acetal groups could be removed by mild acid hydrolysis in aqueous dioxane medium (III).

The biological activity of the various products are being studied at present. These results as well as additional experimental procedures will be reported in due course.

Experimental[7]

N,N-Bis(β-chloroethyl)-2,4-O-benzylidene-3,5-cyclophosphamido-D-ribose Dimethyl Acetal (I).—A dry 500-ml. two-necked flask (A) was connected, *via* a drying tower, to a manometer and an inverted 1000-ml. measuring cylinder for the measurement of hydrogen evolved during the reaction. A was charged with 10 g. of granular sodium metal previously washed with anhydrous ether and dioxane and partially submerged in a constant temperature water bath at 30°. The granular sodium was covered with 50 ml. of anhydrous dioxane and the zero reading on the measuring cylinder taken after temperature equilibriation.

2,4-O-Benzylidene-D-ribose dimethyl acetal[4] (3.41 g., 0.012 mole) in 50 ml. of anhydrous dioxane was added to the mixture in A and the stopper immediately replaced.

(3) M. Smith, G. I. Drummond, and H. G. Khorana, *J. Am. Chem. Soc.*, **83**, 698 (1961).

(4) D. J. J. Potgieter and D. L. Mac Donald, *J. Org. Chem.*, **26**, 3934 (1961).

(5) O. M. Friedman and A. M. Seligman, *J. Am. Chem. Soc.*, **76**, 655 (1954).

(6) O. M. Friedman and E. Boger, *Anal. Chem.*, **33**, 906 (1961).

(7) Microanalyses by the Microanalytical Section, South African Council for Scientific and Industrial Research.

The volume of hydrogen evolved was noted with 5-min. intervals. After 5 hr., when the calculated volume of hydrogen (330 ml.) corresponding to the reaction of two hydroxyl groups with sodium had been evolved, the rate of hydrogen evolution became negligible. The reaction mixture was filtered with suction through a column (2-cm. diameter), packed with glass wool (5 cm.) and Hyflo Super Cel (3 cm.) under anhydrous conditions. The apparatus was washed with anhydrous dioxane and the washings collected with the filtrate (210 ml.). The amount of alkoxide was determined in an aliquot of the filtrate.[8]

The dioxane filtrate (approximately 200 ml. containing 0.0114 mole of alkoxide) was slowly added over a period of 15 min. under anhydrous conditions, with the aid of a dropping funnel, to a mechanically stirred solution of N,N-bis-(β-chloroethyl)phosphamido dichloride[5] (V) (3.0 g., 0.0116 mole) in 50 ml. of anhydrous dioxane in a dried 500-ml. three-necked flask. The reaction mixture was cooled in an ice bath during the addition of the alkoxide. The mixture was left at room temperature under exclusion of aerial moisture.

After 60 hr. a fine white precipitate was collected by centrifugation and shown to consist of sodium chloride (1.55 g., calculated 1.30 g.). The supernatant was concentrated in vacuum at 50°. A light yellow oil, which could not be crystallized, was obtained. The oil was dissolved in anhydrous ether, a small, yellow, insoluble fraction being rejected. The ethereal extract was concentrated in vacuum and the product precipitated with petroleum ether (50–70°). Repeated precipitations from ether–petroleum ether yielded an analytically pure colorless oil (4.8 g.) which could not be crystallized.

Anal. Calcd. for $C_{18}H_{26}O_7NPCl_2$: C, 45.96; H, 5.57; N, 2.97. Nitrogen mustard hydrochloride, 37.95. Found: C, 45.86; H, 5.51; N, 2.47; nitrogen mustard hydrochloride after acid hydrolysis, 38.58.

N,N-Bis-(β-chloroethyl-3,5-cyclophosphamido-D-ribose Dimethyl Acetal (II).—A solution of N,N-bis(β-chloroethyl)-2,4-*O*-benzylidene-3,5-cyclophosphamido-D-ribose dimethyl acetal (I, 4.8 g.) in absolute methanol (50 ml.) was hydrogenated in the presence of 10% palladized charcoal (1.6 g.). Hydrogen was consumed at an initial rate of approximately 3 ml. per min.

After 6 hr., when the calculated volume of hydrogen (458 ml. corrected to S.T.P.) had been taken up, the catalyst was filtered off and the filtrate concentrated in vacuum. The resulting oil could not be obtained analytically pure by precipitation procedures or column chromatography on cellulose. Paper chromatography (butanol–water) revealed that the material consisted of a fast moving (R_f: 0.85) main fraction which could be revealed on paper, after acid hydrolysis, as a single well defined spot by appropriate coloration procedures for reducing sugars, phosphorus, and nitrogen mustard. A slower moving (R_f: 0.38) sugar contaminant, which did not contain phosphorus or nitrogen mustard, could thus far only be removed by means of preparative paper chromatography on a small scale. The purified material obtained in this manner was shown to contain an acetal grouping and to be free of benzylidene groups (ultraviolet spectrum).

Acknowledgment.—We wish to express our sincere thanks to Professor D.J.J. Potgieter for many valuable discussions and for his sustained interest in our work.

(8) A 10-ml. aliquot was diluted with 25 ml. of water and the liberated alkali determined by titration with 0.100 *N* hydrochloric acid (phenolphthalein), 12.6 ml. being required. (Calcd. 11.7 ml.). On the basis of these titration figures and the volume of hydrogen evolved we concluded that both unsubstituted hydroxyl groups in the 2,4-*O*-benzylidene-D-ribose dimethyl acetal had reacted with sodium.

Formation of 1,4-Diphenylcyclohexadiene-1,4 in an Attempted Internal Wittig Reaction

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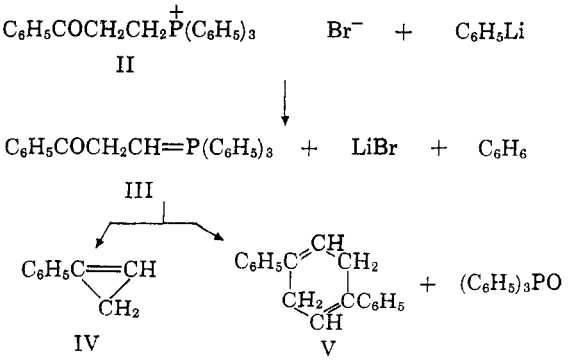
The extremely versatile Wittig reaction[1] between alkylidene phosphoranes and aldehydes and ketones to yield alkenes and phosphine oxides has been applied to the synthesis of a number of cyclic olefins by intermolecular processes.[2] However, only one successful intramolecular Wittig reaction leading to a cyclic product has been recorded; Bieber and Eisman recently reported the formation of 1-phenylcyclopentene by ring closure of the phosphorane derived from triphenyl(4-benzoyl-1-butyl)phosphonium bromide (I).[3] We now wish to report the results of a similar reaction of a lower homolog of I.[4] Triphenyl(2-benzoylethyl)phosphonium bromide (II) prepared by quaternization of β-bromopropiophenone with triphenylphosphine, yielded upon reaction with phenyllithium in benzene an olefin of empirical formula C_9H_8 as the sole isolable product. This olefin showed typical styrene absorption in the ultraviolet (λ_{max} 246 mμ) and infrared bands characteristic of a trisubstituted olefin (786 cm.$^{-1}$) and a phenyl conjugated double bond (1605 cm.$^{-1}$).[5] Two courses for the reaction appeared feasible: intramolecular closure of the phosphorane (III) to yield 1-phenylcyclopropene (IV) or ring formation involving two molecules of III to yield 1,4-diphenylcyclohexadiene-1,4 (V).



On the basis of the well established probability

(1) S. Trippett in "Advances in Organic Chemistry; Methods and Results," Vol. I, edited by R. A. Raphael, E. C. Taylor, and H. Wynberg, Interscience Press, New York, 1960, pp. 83–102.

(2) G. Wittig, H. Eggers, and P. Duffner, *Ann.*, **619**, 10 (1958); K. Dimroth and G. Pohl, *Angew. Chem.*, **73**, 436 (1961); C. E. Griffin, K. R. Martin, and B. E. Douglas, *J. Org. Chem.*, **27**, 1627 (1962).

(3) T. I. Bieber and E. H. Eisman, *ibid.*, **27**, 678 (1962).

(4) This study was undertaken, in part, to develop new methods for the synthesis of 1,2-disubstituted cyclopropenes, N. T. Castellucci and C. E. Griffin, *J. Am. Chem. Soc.*, **82**, 4107 (1960).

(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., John Wiley and Sons, Inc., New York, 1958, pp. 34–52.