Experimental Section[5]

9-β-D-Ribofuranosyl-6-hydroxylaminopurine (II).—9-β-D-Ribofuranosyl-6-chloropurine[6] (I, 2.83 g., 10 mmoles) was dissolved in an ethanol solution of hydroxylamine (350 ml., prepared as indicated in ref. 2), heated at 50° for 6 hr., and then kept at 25° overnight. The crystalline product which deposited was collected and washed with a little cold water and then with ethanol to yield 2.58 g. (90%), m.p. 210–212°. Upon recrystallization from methanol, colorless thin needles, m.p. 218°, $[\alpha]^{25}D$ −57° (*c* 0.5, water), were obtained.

Anal. Calcd. for $C_{10}H_{13}N_5O_5$: C, 42.40; H, 4.59; N, 24.73. Found: C, 42.19; H, 4.86; N, 24.54.

The product (II) gave positive $FeCl_3$ and phosphomolybdate tests, both indicative of the hydroxylamino function. II was recovered unchanged after 3 hr. boiling in water (10% solution) and after heating the same solution at 125° in an autoclave for 1 hr. The solubility of II was 6.9 g./l. of water at 25 ± 1°.

Ultraviolet Spectral Properties.—Compound II exhibited at pH 1.4, λ_{max} 265 mμ (ϵ 17.7 × 10^3); at pH 6.7 (phosphate buffer), λ_{max} 265 mμ (ϵ 14.3 × 10^3); at pH 12.2, λ_{max} 252 mμ,[7] shoulder at 310 mμ; at pH 1.4, λ_{min} 232 mμ (ϵ 3.31 × 10^3); at pH 6.7, λ_{min} 230 mμ (ϵ 4.65 × 10^3); and at pH 12.2, λ_{min} 230 mμ; pK_{a_1} = 3.1 ± 0.1, pK_{a_2} = 9.7 ± 0.1.[8]

Hydrogenation of II.—9-β-D-Ribofuranosyl-6-hydroxylaminopurine (II, 40.0 mg., 0.14 mmole) was dissolved in 95% aqueous ethanol (10 ml.), 5% platinum-on-charcoal catalyst (25 mg.) was added, and the suspension was hydrogenated at 1 atm. at 25°. After uptake of the theoretical volume of H_2, the suspension was filtered, the catalyst was washed with a little ethanol, and the combined filtrates were evaporated to dryness under reduced pressure. The residue was washed with 1 ml. of ethanol and a crystalline product was obtained (34.2 mg., 93%), m.p. 232–234°. The product, which no longer gave the $FeCl_3$ and phosphomolybdate tests, was identified as adenosine (III) by its mixture melting point, ultraviolet spectra at different pH values, and from R_f values in several solvent systems.

(5) Ultraviolet absorption spectra were determined with a Cary recording spectrophotometer, Model 11. Paper chromatograms were run by the ascending method on Schleicher and Schuell No. 1 paper in the following solvent systems: water saturated with 1-butanol; 1-butanol saturated with water (with or without 10% ammonia); 1-butanol–formic acid–water (77:10:13, v./v.). Melting points were taken in a Thomas–Hoover Unimelt apparatus and were corrected. The microanalysis was carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(6) G. B. Brown and V. S. Weliky, *J. Biol. Chem.*, **204**, 1019 (1953); supplied by Cyclo Chemical Corp., Los Angeles, Calif.

(7) The instability of II in alkali prevented precise determination of ϵ.

(8) For comparison, the corresponding values for 6-hydroxylaminopurine determined by titration are pK_{a_1} = 3.80, pK_{a_2} = 9.83, and pK_{a_3} > 12.

N-Substituted Ureidobis(1-aziridinyl)phosphine Oxides

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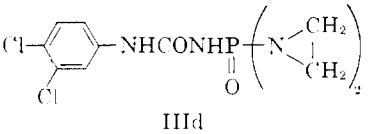
Although some N-substituted ureidobis(1-aziridinyl)-phosphine oxides, $RNHC(O)NHP(O)[NCH_2CHR']_2$ (III), have been reported recently,[1,2] neither a satisfactory method to obtain these difficultly accessible substances has existed so far, nor were the previously prepared representatives of this class sufficiently identified. It has been found that compounds of the general structure III are highly potent chemosterilants,[3] comparable in their biological activity with 2,2,4,4,6,6-hexakis(1-aziridinyl)cyclotriphospha-1,3,5-triene(Apholate) and related compounds.[4]

We have found a convenient method to obtain N-arylureidophosphoryl dichlorides, $RNHC(O)NHP(O)Cl_2$ (II), the precursors of III, by treating isocyanatophosphoryl chloride (I) *in situ* with various (especially aromatic) amines. Equimolar amounts of phosphorus pentachloride and ethyl carbamate in a small volume of ethylene chloride solvent gave I.[5] This solution was utilized directly for the addition reaction with amines without prior removal of the solvent and vacuum distillation. The distillation of I results in partial polymerization and therefore reduction in yield. The direct use of the crude I solution with various amines causes the desired intermediate II to be obtained in higher yields, based on the amount of phosphorus pentachloride employed, and avoids completely the use of the large volume of ether previously necessary for conducting the amine addition reaction.[1]

Table I compiles compounds of the general formula II which have been prepared and utilized for further reaction with aziridines to obtain compounds of structure III. Surprisingly, it has been found that the conversion of II to III can be conducted in aqueous sodium hydroxide solution at −5 to 15°. This method is a distinct advantage over the method in benzene or other anhydrous solvents using tertiary bases as hydrogen chloride acceptors, since it produces a more easily purified crude III free of phosphorus-bonded, ionizable, chlorine-containing contaminants.

The method proved to be especially useful in the synthesis of N-3,4-dichlorophenylureidobis(1-aziridinyl)phosphine oxide (IIId) which was the subject of intensive experimentation.



IIId

The aqueous sodium hydroxide method as well as the benzene–triethylamine method was also used in the preparation of the propylenimine derivative IIIl, another powerful insect chemosterilant of low mammalian toxicity.

In Table II the N-substituted ureidobis(1-aziridinyl)-phosphine oxides of the general structure III which were prepared are given. While most of these compounds do not dissolve readily in ordinary organic solvents, dimethylformamide is suitable in some cases for recrystallization. However, sufficient recovery of large quantities of these chemicals from this solvent is difficult to achieve. Compound IIId, synthesized several times in larger amounts by applying the aqueous alkali method, was obtained in sufficient purity by

(1) A. A. Kropacheva, G. I. Derkach, L. P. Zhuravleva, N. V. Sasonov, and A. V. Kirsanov, *Zh. Obshch. Khim.*, **32**, 5, 1540 (1962).

(2) Z. P. Papanastassiou and T. J. Bardos, *J. Med. Pharm. Chem.*, **5**, 1000 (1962).

(3) Biological data was obtained by Pesticides Research Group, E. R. Squibb Co., Division of the Olin Mathieson Chemical Corp. A comprehensive publication covering these data will appear separately.

(4) R. Rätz and C. Grundmann, U. S. Patent 2,858,306 (Oct. 28, 1958); R. Rätz, E. Kober, C. Grundmann, and G. Ottmann, *Inorg. Chem.*, **3**, 757 (1964).

(5) A. V. Kirsanov and M. S. Marenets, *J. Gen. Chem. USSR*, **31**, 1496 (1961).

TABLE I

N-ARYLUREIDOPHOSPHORYL DICHLORIDES (II)

$Cl_2PONHCONHR$

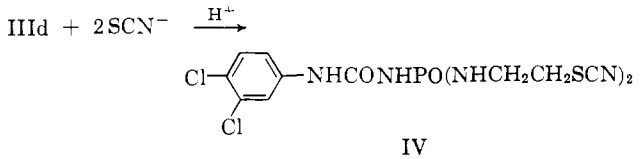
Compd.	R	One-step prepn. Yield, %[a]	One-step prepn. M.p., °C.	Two-step prepn. Yield, %[b]	Two-step prepn. M.p., °C.
a	C_6H_5	91.0	121–122	63.9	122–123
b	2-C_6H_4Cl	49.9	121–122	39.8	118–120
c	4-C_6H_4Cl	83.5	156–157	43.4	147–148
d	3,4-$C_6H_3Cl_2$[c]	84.7	163–164	64.4	163–165
e	2,4-$C_6H_3Cl_2$	76.5	157–158	43.0	157–158
f	2,4,6-$C_6H_2Cl_3$	77.2	156	56.0	157–160
g	4-C_6H_4CN	90.1	170	63.9	163
h	2-$C_6H_4NO_2$	79.5	154–155	62.0	143–145
i	4-$C_6H_4NO_2$	88.1	163	53.4	161
j	4-Cl-2-$NO_2C_6H_3$	75.7	158–160	41.6	152–156
k	1-$C_{10}H_7$	77.4	134	58.7	125

[a] Yield based on amount of PCl_5 used. [b] Yield calculated on the basis of 66.3% yield of distilled Cl_2PONCO and the respective yield in diethyl ether. [c] Infrared absorptions of IId appeared at 2.98 (NH adjacent to aromatic ring), 3.24 (NH adjacent to P=O and C=O), 5.9 (C=O stretch), 6.53 (urea absorption), 8.1 (P=O), 6.3, 6.8, 7.27, 7.7, 8.2, 9.5, 11.3, 11.5, 12.15, and 14.5 (aromatic) μ.

acetone extraction of the crude material. The acetone, however, does not dissolve a small amount of by-product, $C_{11}H_{17}Cl_2N_4O_4P$, m.p. 245°. From a large volume of dioxane, IIId can be successfully recrystallized, leaving this contaminant undissolved. Since the infrared spectrum of this dioxane-insoluble residue is very similar to that of pure IIId, it cannot be detected by infrared spectroscopy in admixture with large amounts of the latter. After its isolation, however, the compound shows hydroxyl absorptions at 3.05 and 9.5 μ. The absence of bands at 7.9 and 12.0 μ indicates disappearance of the aziridine ring with formation of β-hydroxyethylamino groups. Attempted ethylenimine-group titration revealed complete absence of this three-membered ring.

Compounds of the general structure III are insoluble in water. Dilute aqueous alkali, however, dissolves them completely. Their acidic character made it possible to follow effectively the course of their purification. The acid determination was done potentiometrically using aniline as solvent with tetrabutylammonium hydroxide as titrant. The potentiometric inflection obtained with IIId was strong (~300 mv.) and the end point occurred at ~+650 mv.

Aziridine-group titration of IIId was possible with potassium thiocyanate in dimethyl sulfoxide–methanol solution[6] leading to ring cleavage and formation of IV, the latter being isolated as a crystalline substance.



IV

Attempted purification of compounds of the general structure III by neutralization of their aqueous alkaline solution either by dilute mineral or acetic acid was unsuccessful, since the aziridine compounds did not separate unchanged from such solution. In contrast, N-4-cyanophenylureidobis(dimethylamino)phosphine oxide (V), structurally related to IIIg, was readily purified by addition of acetic acid to its dilute sodium hydroxide solution.

(6) R. C. Schlitt, *Anal. Chem.*, **35**, 1063 (1963).

Experimental Section[7]

One-Step Reaction Leading to N-Substituted Ureidophosphoryl Dichlorides (II).—One example of the preparation of a compound of the general formula II, representative of those given in Table I is described.

N-3,4-Dichlorophenylureidophosphoryl Dichloride (IId).—A slurry of 208.3 g. (1.0 mole) of PCl_5 and 60 ml. of ethylene dichloride was placed in a 1-l. three-necked flask equipped with a stirrer, dropping funnel, thermometer, an an Allihn condenser. In the dropping funnel there was placed 89.1 g. (1.0 mole) of ethyl carbamate which was heated by a hot-air stream until molten. The flask was immersed in a mineral oil bath heated to 103°. Addition of molten carbamate was begun and continued at such a rate that the reaction temperature remained between 73 and 81°, while the temperature of the oil bath was kept between 95 and 103°. When the addition of the carbamate was complete, the internal temperature was allowed to rise to 86° and kept there for 10–15 min. The oil bath was removed and the flask contents were allowed to cool to room temperature. An additional portion of 100 ml. of ethylene dichloride was added to the reaction mixture, and a stream of dry nitrogen was bubbled through for 50 min. to ensure the complete removal of the HCl. Then a solution of 162 g. (1.0 mole) of 3,4-dichloroaniline in 350 ml. of ethylene dichloride was added during a period of 15 min. with stirring and external cooling to maintain the internal temperature between 10 and 15°. Fine white solid separated from the solution almost immediately. It was separated by filtration shortly after the amine addition was complete. White powder, 284 g., m.p. 183–184°, was obtained. The yield based on PCl_5 used was 88%.[8]

Anal. Calcd. for $C_7H_5Cl_4N_2O_2P$: N, 8.70; P, 9.62. Found: N, 8.62; P, 9.16.

N-Substituted Ureidobis(1-aziridinyl)phosphine Oxides (III) from N-Substituted Ureidophosphoryl Dichlorides (II) and Aziridines.—The preparation of only one representative of the aziridine compounds listed in Table II is given in detail.

N-3,4-Dichlorophenylureidobis(1-aziridinyl)phosphine Oxide (IIId). Method A. Anhydrous Medium.—In a 500-ml. three-necked flask 9.7 g. (0.037 mole) of the dichloride IId was suspended in 100 ml. of anhydrous ethyl ether. The flask was immersed in an ice bath, and a solution of 3.0 g. (0.070 mole) of ethylenimine and 6.0 g. (0.0595 mole) of triethylamine in 60 ml. of ether was added dropwise with stirring. The separation of a white solid began immediately. The addition required 65 min., and at its completion, the reaction mixture was stirred for an additional 10 min. and finally allowed to stand for 1 hr. The solid was then collected on a Büchner funnel to give 15.0 g. of a mixture of product and triethylamine hydrochloride. This mixture was extracted with two 75-ml. portions of cold water. The re-

(7) All melting points were determined on the plate of a Fisher-Johns block. In the case of compounds III, the sample was placed on a preheated plate at approximately 5° below the melting temperature. Otherwise, because of polymerization, no melting point of these compounds can be determined.

(8) On the basis of the maximum yields for the individual reactions, the best over-all yield obtained in the two-step preparation was 64.4%.

TABLE II: N-ARYLUREIDOBIS(1-AZIRIDINYL)PHOSPHINE OXIDES (III)

Compd.	R	R′	Formula	% yield	M.p., °C.	Calcd., % C	H	Cl	N	P	Found, % C	H	Cl	N	P	% of nonviable housefly eggs[a] Concn. of compd., % 0.025	0.1
a	C_6H_5	H	$C_{11}H_{15}N_4O_2P$	45.5	209	49.62	5.68		21.05	11.63	49.28	5.76		20.19	11.46	70	98
b	2-C_6H_4Cl	H	$C_{11}H_{14}ClN_4O_2P$	41.6	177	43.94	4.69	11.79	18.63	10.30	43.82	5.10	11.80	18.92	10.66	40	98
c	4-C_6H_4Cl	H	$C_{11}H_{14}ClN_4O_2P$	45.0	211	43.94	4.69	11.79	18.63	10.30	43.90	4.88	11.80	18.75	10.68	71	99
d	3,4-$C_6H_3Cl_2$	H	$C_{11}H_{13}Cl_2N_4O_2P$	59.3	203	39.40	3.88	21.11	16.72	9.25	39.10	4.05	21.5	16.39	9.26	99	99
e	2,5-$C_6H_3Cl_2$	H	$C_{11}H_{13}Cl_2N_4O_2P$	66.7	172	39.40	3.88		16.72	9.25	39.23	3.89		16.77	8.90	52	77
f	2,4,6-$C_6H_2Cl_3$	H	$C_{11}H_{12}Cl_3N_4O_2P$	13.5	202				15.17	8.39				14.43	7.77	65	98
g	4-C_6H_4CN	H	$C_{12}H_{14}N_5O_2P$	57.9	222	49.49	4.85		24.05	10.63	48.23[c]	5.28		23.61	10.59	95	100
h	2-$C_6H_4NO_2$	H	$C_{11}H_{14}N_5O_4P$	82.3	160	42.45	4.53		22.50		42.44	5.18		22.22		98	98
i	4-$C_6H_4NO_2$	H	$C_{11}H_{14}N_5O_4P$	69.4	201	42.45	4.53		22.50	9.95	41.08[c]	4.67		20.96	9.95	70	96
j	4-Cl-2-$NO_2C_6H_3$	H	$C_{11}H_{13}ClN_5O_4P$	83.3	188	38.22	3.79			8.96	38.35	3.72			8.49	18	97
k	1-$C_{10}H_7$	H	$C_{15}H_{17}N_4O_2P$	58.5	156				17.71	9.79				16.67	9.48	24	54
l	3,4-$C_6H_3Cl_2$	CH_3	$C_{13}H_{17}Cl_2N_4O_2P$	31.7	174	42.99	4.72	19.52	15.43	8.53	42.93	4.77	19.5	15.92	8.53	95	100
m	2-$C_6H_4NO_2$	CH_3	$C_{12}H_{18}N_5O_4P$	87.2	140	46.02	5.35				45.70	5.70					69
																76	98 (Aphoxite)

[a] For the type of screening test, see G. C. La Breeque and H. K. Gouck, *J. Econ. Entomol.*, **56**, 476 (1963). [b] Infrared absorptions appeared (for IIId) at 3.02, 3.3 (NH stretch), 5.9 (C=O), 6.5 (urea bond), 7.9 (aziridine ring), 8.5 (P=O stretch), 6.3, 6.8, 7.2, 7.7, 8.8, 9.5, 11.6, and 12.15 (aromatic) μ, and (for III) at 3.1 (NH stretch), 5.9 (C=O), 6.5 (urea bond), 8.0 (aziridine ring), 8.5 (P=O stretch), 6.3, 6.8, 7.2, 7.7, 8.7, 9.6, 11.5, and 12.2 (aromatic) μ. [c] Solvent-washed samples were analyzed.

filtered residue was treated with cold acetone, filtered, and dried *in vacuo* (P_2O_5); yield, 35.4%. Elemental analysis indicated that the acetone-insoluble material was the desired IIId. After recrystallization from dimethylformamide, the colorless prismatic crystals melted at 192°, followed by polymerization. The elemental analyses of both the acetone-washed, nonrecrystallized and the dimethylformamide-recrystallized product are given.

Anal. Calcd. for $C_{11}H_{13}Cl_2N_4O_2P$: C, 39.42; H, 3.91; N, 16.72; P, 9.24. Found (acetone-washed product): C, 38.56; H, 4.74; N, 16.19; P, 8.83. Found (dimethylformamide-recrystallized product): C, 39.07; N, 4.55; N, 16.63; P, 9.24.

Method B. Aqueous Medium.—A solution of 24.0 g. (0.6 mole) of NaOH and 28.1 g. (0.653 mole) of ethylenimine in 300 ml. of water was cooled to −14°. To this was added 93.0 g. (0.29 mole) of the dichloride IId in portions of approximately 5 g. each with stirring so that the temperature was kept below −2°. After standing for 15 min. at ambient temperature, the white reaction product was collected on a Büchner funnel. It was washed with distilled water, dried (P_2O_5), washed with acetone, and redried to give 57.4 g. (59.3%) of white crystalline powder, m.p. 190° followed by polymerization. Analysis of the acetone-washed product is given.

Anal. Calcd. for $C_{11}H_{14}Cl_2N_4O_2P$: C, 39.42; H, 3.91; Cl, 21.11; N, 16.72; P, 9.24. Found: C, 39.10; H, 4.05; Cl, 21.50; N, 16.39; P, 9.26.

A 20-g. sample of this acetone-washed material was refluxed in 320 ml. of dioxane for approximately 5 min., whereupon the bulk of the material went into solution. Insolubles were removed by filtering the hot solution through a Büchner funnel (0.7 g.). To the clear filtrate 200 ml. of petroleum ether (b.p. 65–110°) was added and this solution allowed to stand overnight. The amount of 17.0 g. of colorless crystals, m.p. 203°, was recovered by vacuum filtration; proton assay by titration with tetrabutylammonium hydroxide gave 100.1 and 99.2%; imine assay by KSCN titration gave 98.8 and 99.6%.

Anal. Calcd. for $C_{11}H_{13}Cl_2N_4O_2P$: C, 39.42; H, 3.91; Cl, 21.16; N, 16.72; P, 9.24. Found: C, 39.68; H, 3.97; Cl, 21.10; N, 16.91; P 9.11.

The dioxane-insoluble material was extracted twice with 10-ml. portions of boiling dioxane to give a product, m.p. 245° dec., with no prior melting on a 200° preheated plate. It was free of ionizable chlorine, but no suitable solvent could be found for its recrystallization. Therefore, it was analyzed in its crude form. Imine assay titration with KSCN revealed the absence of aziridine rings.

Anal. Calcd. for $C_{11}H_{15}Cl_2N_4O_4P$: C, 35.60; H, 4.62; Cl, 19.11; N, 15.10; P, 8.35. Found: C, 35.44; H, 4.57; Cl, 17.60; N, 14.06; P, 8.57.

N-4-Cyanophenylureidobis(dimethylamino)phosphine Oxide (V).—The amount of 5.5605 g. (0.020 mole) of N-4-cyanophenylureidophosphoryl dichloride was added in small portions to a solution of 1.6007 g. (0.040 mole) of NaOH and 7.5713 g. (0.042 mole) of a 25% aqueous solution of dimethylamine and 7 ml. of distilled water while the reaction temperature was kept between −10 and −5°. A solid separated immediately which was broken up and stirred. The mixture was allowed to stand in the cold for 35 min. The white solid was separated by filtration and dissolved in dilute NaOH solution from which it was reprecipitated as colorless crystals by means of acetic acid, m.p. 193°.

Anal. Calcd. for $C_{12}H_{18}N_5O_2P$: C, 48.81; H, 6.14; N, 23.72; P, 10.49. Found: C, 48.27; H, 5.86; N, 23.03; P, 10.30.

N-3,4-Dichlorophenylureido(bis-N-β-thiocyanatoethylamino)-phosphine Oxide (IV).—One gram of IIId was dissolved in 20 ml. of dimethyl sulfoxide, using an ultrasonic generator and a transducerized tank. The solution was allowed to stand for 30 min. and 50 ml. of a 16% (w./v.) solution of potassium thiocyanate in methanol was added with stirring, followed by addition of 20 ml. of a 7.3% (w./v.) solution of *p*-toluenesulfonic acid in methanol containing 5% water. The reaction mixture was subsequently diluted with 200 ml. of distilled water and the excess acid was neutralized with methanolic KOH. The resulting precipitate was filtered through a coarse-porosity fritted-disk funnel, washed with water, and dried for 8 hr. at 40° in a vacuum oven; yield, 0.7 g. (52%) of small colorless needles; m.p. 132–133°. The infrared spectrum shows powerful absorptions at 3.0 (NH), 4.65 (SCN), and 7.72 μ (P=O).

Anal. Calcd. for $C_{13}H_{15}Cl_2N_6O_2PS_2$: C, 34.20; H, 3.29; Cl, 15.54; N, 18.35; P, 6.79. Found: C, 34.44, 34.44; H, 3.40, 3.42; Cl, 16.10, 16.20; N, 18.33, 18.37; P, 6.79, 6.87.