**1,3-Bis(*p*-anisyl)propene.**—1,3-Bis(*p*-anisyl)-2-propanone was prepared from *p*-anisylacetic acid and lead carbonate.[18] Reduction of the above ketone with lithium aluminum hydride in tetrahydrofuran at 25° afforded 1,3-bis(*p*-anisyl)-2-propanol in 91% yield as needles, mp 56.5–57.5°.

*Anal.* Calcd for $C_{17}H_{20}O_3$: C, 74.96; H, 7.41. Found: C, 74.60; H, 7.24.

Reaction of the above alcohol with *p*-toluenesulfonyl chloride in pyridine[16] afforded 1,3-bis(*p*-anisyl)-2-propanol *p*-toluenesulfonate in 85% yield as needles, mp 99–99.5° (methanol).

*Anal.* Calcd for $C_{24}H_{26}O_5S$: C, 67.59; H, 6.15; S, 7.50. Found: C, 67.85; H, 6.19; S, 6.48.

The above toluenesulfonate was refluxed in *tert*-butyl alcohol containing excess potassium *tert*-butoxide to afford 1,3-bis(*p*-anisyl)propene in 84% yield as needles: mp 66.5–67° (methanol); nmr ($CDCl_3$) δ 6.4 (A part of $ABX_2$, $J_{AB}$ = 15.5 Hz, 1 H, ArC**H**=CHCH$_2$Ar), 6.18 (B part of $ABX_2$, $J_{AB}$ = 15.5 Hz, $J_{BX}$ = 5.5 Hz, 1 H, ArCH=C**H**CH$_2$Ar), 3.4 (X part of $ABX_2$, $J_{BX}$ = 5.5 Hz, 2 H, ArCH=CHC**H**$_2$Ar).

*Anal.* Calcd for $C_{17}H_{18}O_2$: C, 80.27; H, 7.14. Found: C, 80.29; H, 6.90.

**Formation of Lithium Salts of Carbon Acids.**—The following procedure is typical. To a stirred solution of 208 mg (1.0 mmol) of dibenz[*b*,*g*]oxocin in 5 ml of dry tetrahydrofuran at −80° (Dry Ice–acetone) under nitrogen was added 0.5 ml (1.05 mmol) of 2.1 *M* butyllithium in hexane. A red precipitate was formed. The mixture was stirred for 10 min, the cooling bath was removed, and the now homogeneous solution was allowed to stand at 25° for 4.5 hr. The red solution was added dropwise to a rapidly stirred solution of 4 ml of deuterium oxide (99.77% isotopic purity) in 2.5 ml of tetrahydrofuran. Work-up afforded 204 mg of an oil that was distilled at 55° (0.5 mm) to afford 177 mg of a clear oil. Low-voltage mass spectrometry afforded the isotopic content: 12% $d_0$, 82% $d_1$, 6% $d_2$. The area of the nmr peak at ε 3.34 corresponded to 1 H and the splitting pattern to the part structure ArCH=CHCHDAr.

**Equilibration of Anions.**—The following experiment is typical. To a solution of 127 mg (0.50 mmol) of 1,3-bis(*p*-anisyl)propene in 2.5 ml of dry tetrahydrofuran at −80° was added 0.235 ml (0.50 mmol) of 2.13 *M* butyllithium in hexane. The pink reaction mixture was stirred at −80° for 10 min and allowed to stand at 25° for 3.5 hr. A solution of 104 mg (0.50 mmol) of dibenz[*b*,*g*]oxocin in 1.5 ml of tetrahydrofuran was added, and the mixture was stirred for 25 min and then added to a mixture of 3 ml of deuterium oxide and 2.5 ml of tetrahydrofuran. Work-up afforded 227 mg of a sticky solid. Low-voltage mass spectrometry of this mixture afforded the following results: dianisylpropene (*m/e* 254–256), 97% $d_0$, 3% $d_1$; dibenzoxocin (*m/e* 208–212), 24% $d_0$, 74% $d_1$, 2% $d_2$. Recrystallization and distillation of this mixture allowed separation of the two olefins, low-voltage mass spectra of which indicated the same isotopic distribution as above. The results for the series of experiments are in Table II.

**Registry No.**—**1**, 24974-26-3; **3**, 34414-43-2; **4**, 34414-44-3; **5**, 34414-45-4; **5** methanesulfonate, 34414-50-1; **7**, 34414-46-5; **8**, 34414-47-6; **9**, 34414-48-7; 10-oxo-9,10-dihydrodibenz[*b*,*g*]oxocin, 34414-49-8; 1,3-bis(*p*-anisyl)-2-propanol, 34414-51-2; 1,3-bis(*p*-anisyl)-2-propanol *p*-toluenesulfonate, 24573-54-4; 1,3-bis(*p*-anisyl)propene, 34414-53-4.

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# Aminoethylation of Some Pyrimidine Derivatives[1]

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Ethylenimine alkylated readily and exclusively the $N^1$ and $N^3$ positions of 2,4-dioxopyrimidine derivatives. Substitution of ethylenimine by 2-chloroethylamine produced lower yields. The reactivity of several other nucleic acid building blocks was investigated. The structures were assigned on the basis of spectral data and on the results of hydrolysis.

In aqueous ethylenimine, $HN(CH_2)_2$, 4-thiouridine is the most readily modified base[2] at pH 8 but the modification is not absolutely specific in that a slower alkylation of guanine residues in *E. coli* B tRNA is also detectable.[3]

This paper presents the evidence that under more drastic conditions $HN(CH_2)_2$ alkylates readily and exclusively the $N^1$ and $N^3$ positions of 2,4-dioxopyrimidine derivatives. The highest yields were obtained when pyrimidines were directly dissolved in $HN(CH_2)_2$; dilution with water or with organic solvents decreased yields considerably.

Compounds 3-(2-aminoethyl)uridine (**5**) and 3-(2-aminoethyl)thymidine (**9**) were isolated from the reaction mixture of uridine (**1**) or thymidine (**3**) in yields of over 70%; less than 10% of nucleosides were recovered unchanged; the rest comprised a mixture of higher alkylated derivatives.

The presence of alkyl at the $N^3$ position of **5** and **9** was indicated by the uv spectra; comparison was made with spectra of known 3-alkyl nucleosides. The presence of two strong bands in the carbonyl region in the ir spectra of aminoethylated derivatives excluded O-alkylation. The assigned structures were confirmed by acidic hydrolysis of **5** and **9** to 3-(2-aminoethyl)-uracil (**6**) and 3-(2-aminoethyl)thymine (**10**), respectively. No unsubstituted pyrimidines were obtained after hydrolysis. This would have been the case if the O-alkylation of sugar moiety or the acid-labile O-alkylation on the heterocyclic ring had occurred.[4]

Deoxyuridine, 2′,3′-*O*-isopropylideneuridine, and 5′-*O*-tritylthymidine reacted like the corresponding parent compounds, whereas 3-methyluridine and 3-methylthymidine were, as expected, quantitatively recovered from the reaction mixture.

A small amount of higher alkylated derivatives was present in all reaction products. It was proven by chemical and spectroscopic means that these compounds are oligomers of $HN(CH_2)_2$ attached to the $N^3$ position of nucleosides. Some polymerization of $HN(CH_2)_2$

(1) Presented in part at the 6th Middle Atlantic Regional Meeting of the American Chemical Society, Baltimore, Md., Feb 1971.

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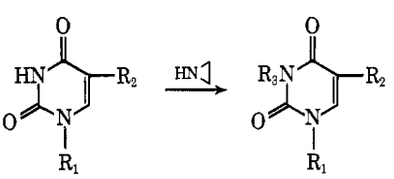
to low molecular weight products was catalyzed by 2,4-dioxopyrimidine derivatives, and hence freshly distilled reagent decreased only moderately the formation of 3-oligoethylenimino derivatives.

The N-alkylation of pyrimidine bases was complicated by the fact that these systems possess two ionizable protons. Thus, uracil (**2**) ($pK_a$ $N^1$ = 9.43; $pK_a$ $N^3$ > 13[5]) gave rise to approximately equal amounts of 1-(2-aminoethyl)uracil (**7**) and 1,3-di(2-aminoethyl)-uracil (**8**), whereas the 3-alkylated derivative **6** was isolated as a minor product. It is not possible to obtain $N^1$-substituted product selectively, since in the $N^1$-monosubstituted product the acidity of the $N^3$ proton is increased sufficiently ($pK_a$ = 9.71[6]) to give a competitive dialkylation reaction, namely, formation of **8**. Corresponding derivatives (**11**, **12**, and **10**) were synthesized from thymine (**4**). The relatively low yields encountered in both cases were caused by the extensive polymerization of $HN(CH_2)_2$.

Two pairs of structural isomers (**13**, **14** and **15**, **16**) of the single site dialkylated pyrimidines are possible, and both were isolated and tentatively identified by uv spectroscopy and correct analysis for N, and corroborated by the following chemical properties. In line with the findings of Rogers, *et al.*,[7] the $N^1$- and $N^3$-alkylated uracils (**6**, **7**, **13**, **14**) were found to be stable when heated with dilute NaOH. Under the same reaction conditions, the 1,3-dialkylated uracil (**8**), the 3-alkylated uridine (**5**), and the model compound 3-methyluridine were partly degraded. This is in accord with the reported instability of 1,3-dialkyluracils in alkali.[8] Under the above conditions, all derivatives of thymine (**9**, **10**, **11**, **12**, **15**, **16**) and the model com-



1-4 5-16

| | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| 1 | Ribosyl | H | |
| 2 | H | H | |
| 3 | 2-Deoxyribosyl | Me | |
| 4 | H | Me | |
| 5 | Ribosyl | H | $H_2NCH_2CH_2$ |
| 6 | H | H | $H_2NCH_2CH_2$ |
| 7 | $H_2NCH_2CH_2$ | H | H |
| 8 | $H_2NCH_2CH_2$ | H | $H_2NCH_2CH_2$ |
| 9 | 2-Deoxyribosyl | Me | $H_2NCH_2CH_2$ |
| 10 | H | Me | $H_2NCH_2CH_2$ |
| 11 | $H_2NCH_2CH_2$ | Me | H |
| 12 | $H_2NCH_2CH_2$ | Me | $H_2NCH_2CH_2$ |
| 13 | $H(NHCH_2CH_2)_2$ | H | H |
| 14 | H | H | $H(NHCH_2CH_2)_2$ |
| 15 | $H(NHCH_2CH_2)_2$ | Me | H |
| 16 | H | Me | $H(NHCH_2CH_2)_2$ |

pound, 3-methylthymidine, were stable in alkali. This is in agreement with the known fact that 3-methylthymidine is stable,[9] while the $O^2$- and $O^4$-glucosides of thymine and uracil are hydrolyzed completely when heated with 0.2 *N* NaOH at 100° for 10 min to give thymine and uracil, respectively.[7]

The additional and definite proof of structure of 1,3-dialkylated pyrimidines **8** and **12** has involved the unambiguous primary synthesis starting with 1- and 3-monoalkylated pyrimidines **6**, **7**, **10**, and **11**.

In all four cases the isolated dialkylated compounds were identical by mixture melting point, uv spectroscopy, and paper and ion-exchange chromatography with **8** or **12** synthesized from unsubstituted pyrimidines **2** or **4**.

In line with expectation, preliminary experiments indicated that 2′-deoxyuridine, pseudouridine, and inosine reacted very readily with $HN(CH_2)_2$, whereas cytidine resisted alkylation. Adenosine and deoxyadenosine were quantitatively recovered unchanged from the reaction mixture, and the bases cytosine, adenine, and guanine remained insoluble in $HN(CH_2)_2$.

Aminoethylation of pyrimidines with a 2-mol excess of 2-chloroethylamine in a basic aqueous solution produced lower yields. This is to be expected, since the reaction proceeds through the ethylenimine intermediate.[10] A large excess of $ClCH_2CH_2NH_2$ did not significantly increase the yield owing to a ready polymerization of this reagent in an aqueous basic solution.

In all cases the products have been *N*-alkylpyrimidine derivatives; this is based on the analytical and spectroscopic data, and on the results of base and acid hydrolysis.

Alkylation with $ClCH_2CH_2NH_2$ in DMSO under anhydrous reaction conditions was unsuccessful. Condensation of 2-aminoethanol with uracil in the presence or in the absence of a condensing agent[11] led to an unidentified compound.

## Experimental Section[12]

The ion-exchange resins used were Dowex 1 × 8 and Dowex 50W × 8, both 200–400 mesh, and Duolite C-20, 20–50 mesh.

Purity of the compounds was checked by descending chromatography on Whatman No. 1 paper. Solvent systems used were (A) *i*-PrOH–HCl–$H_2O$ (680:164:156, v/v); (B) *n*-BuOH–AcOH–$H_2O$ (4:1:1, v/v); (C) *n*-BuOH–$H_2O$ (86:14, v/v); (D) *i*-PrOH–$NH_4OH$–$H_2O$ (7:1:2, v/v). The compounds were located by their absorption of uv light, or were visualized as purple spots on paper chromatograms with ninhydrin spray.

**General Procedure for Aminoethylation of Pyrimidines with Ethylenimine.**—A solution of 1.0 g of pyrimidine derivative in 10 ml of $HN(CH_2)_2$ was incubated at 37° for 2 days and then it was concentrated to a gum over $H_2SO_4$ *in vacuo*. The crude aminoethylated derivative, contaminated with starting material, polyethylenimines, and polyethyleniminopyrimidines, was purified as indicated below.

**3-(2-Aminoethyl)uridine (5). Method A.**—The reaction product of $HN(CH_2)_2$ and uridine (**1**) was dissolved in about 50 ml of water and applied on a 0.9 × 65 cm column of Dowex 50W ($NH_4^+$) resin. Elution was carried out with 0.05 *M* $NH_4OH$, and optical density of the effluent was measured at 260 nm. Unreacted **1** (40 mg, 4%) was eluted in the first 150 ml. The fractions containing **5** (800–1800 ml) were concentrated to dryness and $NH_4HCO_3$ was removed by repeated coevaporation with small amounts of water. The slightly colored residue was redissolved in about 50 ml of water and passed through a column of

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0.5 ml of Dowex 1 ($HCO_3^-$). The colorless effluent was concentrated to dryness and the residue was crystallized from 95% EtOH to give 0.89 g (76%). At least eight small peaks of 3-polyethyleniminouridines could still be eluted from the column with 1.5 *M* $NH_4OH$.

When starting with 200 mg of uridine, the purification was conveniently performed on a 1 × 3 cm column of Dowex 50W ($H^+$) resin. The unreacted **1** was washed out with 20 ml of $H_2O$, and then **5** was eluted with 15 ml of 1.5 *M* $NH_4OH$. The eluate was concentrated to dryness and the residue was crystallized consecutively from 95, 50, and 95% EtOH as needles: yield 100 mg (43%); decomposition above 170°; $R_f$ (A) 0.34; uv max (pH 2) 262 nm, min 232 nm, max (pH 12) 262 nm, min 233 nm; ir (KBr) 1710 and 1670 $cm^{-1}$ (CO). *Anal.* Calcd for $C_{11}H_{17}N_3O_6$: C, 45.99; H, 5.96; N, 14.63. Found: C, 45.85; H, 6.16; N, 14.63. Compound **5** in supernatant fractions can be conveniently separated from polyethyleniminouridines by paper chromatography (Whatman 3MM) in solvent A.

**Method B.**—The reaction product of $HN(CH_2)_2$ and 2′,3′-*O*-isopropylideneuridine, 3-(2-aminoethyl)-2′,3′-*O*-isopropylideneuridine, was hydrolyzed in 1 *N* HCl at 80° for 10 min. The resulting compound, after being purified, was found to be identical with **5** by chromatographic properties, uv spectra, melting point, and mixture melting point.

**3-(2-Aminoethyl)uracil (6).**—Compound **5** (300 mg) was hydrolyzed in 5 ml of 70% $HClO_4$ for 2 hr at 100°, diluted with 10 ml of $H_2O$, and centrifuged off the tar. The supernate and washings (2 × 10 ml) were neutralized with 6.0 g of KOAc, and the precipitated $KClO_4$ was removed by filtration. The filtrate was concentrated to dryness *in vacuo* and **6** was extracted from the residue with 95% EtOH. After concentration to dryness, the residue was dissolved in about 30 ml of $H_2O$ and applied on a 3 × 1 cm column of Dowex 50W ($H^+$) resin. Impurities were washed out with $H_2O$, **6** was eluted with 0.05 *M* $NH_4OH$, and eluate was passed through 1-ml Dowex 1 ($HCO_3^-$) resin. Concentration of effluent to dryness and crystallization from EtOH gave 147 mg (91%) of **6** as an amorphous powder, mp 162–165°, $R_f$ (A) 0.30.

**6**·HCl was obtained as off-white crystals (90% EtOH): mp 234–235° dec; uv max (pH 2) 260 nm, min 230 nm, max (pH 12) 284 nm, min 245 nm; ir (KBr) 1620 and 1600 $cm^{-1}$ (CO); nmr ($D_2O$) δ 7.64 (d, 1, *J* = 8 Hz, $C_6H$), 5.95 (d, 1, *J* = 8 Hz, $C_5H$), 4.33 (t, 2, *J* = 6 Hz, $N_3CH_2$), 3.43 (t, 2, *J* = 6 Hz, $CH_2NH_2$). *Anal.* Calcd for $C_6H_9N_3O_2$·HCl: C, 37.61; H, 5.26; N, 21.93; Cl, 18.50. Found: C, 37.66; H, 5.35; N, 21.64; Cl, 18.45.

**1-(2-Aminoethyl)uracil (7) and 1,3-Di(2-aminoethyl)uracil (8).**—The concentrated reaction product of uracil (**2**) and $HN(CH_2)_2$ was dissolved in about 50 ml of 0.5 *M* HOAc, applied on a 1.4 × 68 cm column of Dowex 50 ($H^+$) resin, and eluted with 6 l. of a linear gradient from 0 to 3 *N* HCl. Unreacted **2** was eluted in the first peak (fractions 4–21, 20 ml/fraction), followed by **7** (fractions 75–102), **8** (fractions 187–227), and polyethyleniminouridines (fractions 267–300). Peaks were concentrated to dryness, the residues were discolored by passage of aqueous solutions through columns of 0.5 ml Dowex 1 ($Cl^-$) resin, and the effluents were concentrated to dryness. The isolated hydrochlorides were crystallized from 90% EtOH: yield of **7**·HCl 186 mg (10.9%), off-white crystals, decomposition above 220°; $R_f$ (A) 0.28; uv max (pH 2) 262 nm, min 230 nm, max (pH 12) 265 nm, min 242 nm; ir (KBr) 1730 and 1680 $cm^{-1}$ (CO); nmr ($D_2O$) δ 7.77 (d, 1, *J* = 8 Hz, $C_6H$), 5.93 (d, 1, *J* = 8 Hz, $C_5H$), 4.23 (t, 2, *J* = 6 Hz, $N_1CH_2$), 3.48 (t, 2, *J* = 6 Gz, $CH_2NH_2$). *Anal.* Calcd for $C_6H_9N_3O_2$·HCl: C, 37.61; H, 5.26; N, 21.93; Cl, 18.50. Found: C, 37.54; H, 5.37; N, 21.65; Cl, 18.34. The HCl-free **7**, mp 170–172° (EtOH), was obtained by elution from Dowex 50W ($NH_4^+$) resin with 0.1 *M* $NH_4OH$: yield of **8**·2HCl 261 mg (10.8%), decomposition above 250°; $R_f$ (A) 0.19; uv max (pH 2) 264 nm, min 232 nm, max (pH 12) 268 nm, min 236 nm; ir (KBr) 1710 and 1670 $cm^{-1}$ (CO); nmr ($D_2O$) δ 7.73 (d, 1, *J* = 8 Hz, $C_6H$), 6.01 (d, 1, *J* = Hz, $C_5H$), 4.28 (m, 4, $N_1$-$CH_2$ and $N_3CH_2$), 3.44 (m, 4, two $CH_2NH_2$). *Anal.* Calcd for $C_8H_{14}N_4O_2$·2HCl: C, 35.44; H, 5.95; N, 20.66; Cl, 26.15. Found: C, 35.35; H, 6.08; N, 20.38; Cl, 25.92. The HCl-free **8** was isolated by means of ion-exchange resin in the form of noncrystallizable gum. The mother liquor from **7**·HCl contained **6**. This mixture was resolved on a 1.4 × 68 cm column of Dowex 50W ($NH_4^+$) resin using for elution 6 l. of linear gradient from 0 to 0.15 *M* $NH_4OH$. Compound **7** was eluted in the first peak; the second peak contained 18 mg (1.3%) of **6**.

**3-(2-Aminoethyl)thymidine (9). Method A.**—The reaction product of $HN(CH_2)_2$ and thymidine (**3**) was purified by the procedure described for the preparation of **5**, except that the first crystallization was from acetone–EtOH, then from EtOH, as needles, yield 0.95 g (72%, calculated as $\cdot{}^1/_2C_5H_8$[13]).

**Method B.**—The reaction product of $HN(CH_2)_2$ and 5′-*O*-tritylthymidine was washed with $H_2O$, and then the water-insoluble 3-(2-aminoethyl)-5′-*O*-tritylthymidine was extracted with MeOH and detritylated by heating for 10 min at 100° in 80% HOAc. The isolated compound, identical with **9** prepared above, was obtained as needles: decomposition above 160°; $R_f$ (A) 0.53; uv max (pH 2) 268 nm, min 237 nm, max (pH 12) 268 nm, min 238 nm; ir (KBr) 1690 and 1670 $cm^{-1}$ (CO). *Anal.* Calcd for $C_{12}H_{19}N_3O_5\cdot{}^1/_2C_5H_8$: C, 54.53; H, 7.26; N, 13.16. Found: C, 54.55; H, 7.28; N, 13.23.

**3-(2-Aminoethyl)thymine (10).**—Compound **9** (300 mg) was hydrolyzed in 5 ml of HOAc–HCl (2:1, v/v) at 100° for 1 hr, then concentrated to dryness over NaOH *in vacuo*. The residue was freed from decomposition products by passage of the aqueous solution through 0.5 ml of Dowex 1 ($Cl^-$) resin and the effluent was applied on 1 ml of Dowex 50 ($H^+$) resin. The derivative was eluted with 1 *N* HCl, concentrated to dryness, and crystallized from 95% EtOH to give 186 mg (96%) of **10**·HCl: mp 221–223°; $R_f$ (A) 0.41; uv max (pH 2) 265 nm, min 235 nm, max (pH 12) 291 nm, min 249 nm; ir (KBr) 1720 and 1670 $cm^{-1}$ (CO); nmr ($D_2O$) δ 7.49 (s, 1, $C_6H$), 4.34 (t, 2, *J* = 6 Hz, $N_3CH_2$), 3.41 (t, 2, *J* = 6 Hz, $CH_2NH_2$), 1.95 (s, 3, $C_5CH_3$). *Anal.* Calcd for $C_7H_{11}N_3O_2$·HCl: C, 40.88; H, 5.88; N, 20.43; Cl, 17.24. Found: C, 40.88; H, 5.90; N, 20.14; Cl, 17.22. The HCl-free **10** was obtained by means of cation-exchange resin as needles from EtOH–acetone, mp 171–172°.

**1-(2-Aminoethyl)thymine (11) and 1,3-Di(2-aminoethyl)-thymine (12).**—Compounds **11** and **12** were isolated from the reaction mixture of thymine and $HN(CH_2)_2$ by the procedure described for the preparation of **7** and **8**, yield of **11**·HCl 283 mg (17.4%). The supernatant contained 40 mg of **11**·HCl and 35 mg (2.2%) of **10**·HCl. Compound **11**·HCl decomposed above 200°: $R_f$ (A) 0.35; uv max (pH 2) 269 nm, min 235 nm, max (pH 12) 270 nm, min 245 nm; ir (KBr) 1700 and 1680 $cm^{-1}$ (shoulder, CO); nmr ($D_2O$) δ 7.63 (s, 1, $C_6H$), 4.23 (t, 2, *J* = 6 Hz, $N_1CH_2$), 3.51 (t, 2, *J* = 6 Hz, $CH_2NH_2$), 1.93 (s, 3, $C_5$-$CH_3$). *Anal.* Calcd for $C_7H_{11}N_3O_2$·HCl: C, 40.88; H, 5.88; N, 20.43; Cl, 17.24. Found: C, 40.98; H, 5.80; N, 20.14; Cl, 17.15. The HCl-free **11**, obtained as needles (EtOH), mp 191–192°, sublimed at higher temperature. They ield of **12**·2HCl was 575 mg (25.4%): decomposition above 250°; $R_f$ (A) 0.29; uv max (pH 2) 269 nm, min 236 nm, max (pH 12) 272 nm, min 240 nm; ir (KBr) 1700 and 1670 $cm^{-1}$ (CO); nmr ($D_2O$) δ 7.58 (s, 1, $C_6H$), 4.27 (m, 4, $N_1CH_2$ and $N_3CH_2$), 3.42 (m, 4, two $CH_2NH_2$), 1.96 (s, 3, $C_5CH_3$). *Anal.* Calcd for $C_9H_{16}N_4O_2$·2HCl: C, 37.91; H, 6.36; N, 19.65; Cl, 24.86. Found: C, 38.09; H, 6.40; N, 19.44; Cl, 24.71. The HCl-free **12** was isolated as a gum; all attempts to crystallize it failed.

Small-scale separations of **10**, **11**, and **12** as well as **6**, **7**, and **8** could be conveniently performed by paper chromatography (solvent A, 80 hr).

**Reaction of Other Pyrimidines and Purines with Ethylenimine.**—The same reaction conditions were used except that the amounts were scaled down. The reaction progress was followed by means of paper and ion-exchange chromatography.

**Reaction of $N^1$- and $N^3$-Monoaminoethylated Pyrimidines with Ethylenimine.**—Compounds **6**, **7**, **10**, and **11** were treated with $HN(CH_2)_2$ under reaction conditions specified by the general procedure and the concentrated reaction products were applied on columns of Duolite C-20 ($H^+$) resin (1 × 25 cm). The unreacted monoalkylated compounds were eluted with 0.1 *M* $NH_4OH$ and then the 1,3-dialkylated pyrimidines (**8**, **12**), with traces of trialkylated derivatives, were eluted with 1.5 *M* $NH_4OH$ and purified by paper chromatography in solvent A: yields, **8**, 75–80%; **12**, 60–65%.

**Aminoethylation of Uracil (2) and Thymine (4) with 2-Chloroethylamine.**—To a boiling solution of 10 ml of 1 *N* NaOH, 100 mg of KI, 2 ml of $Et_3N$, and 1.12 g (10 mmol) of **2** or 1.26 g (10 mmol) of **4**, was added dropwise in a 4-hr period a solution of 2.32 g (20 mmol) of $ClCH_2CH_2NH_2$·HCl in 20 ml of 1 *N* NaOH. The cooled reaction mixture was applied on a 1.5 × 28 cm column of Duolite C-20 ($H^+$) resin. The unreacted pyrimidine (0.81 g of **2**, 0.69 g of **4**) was washed out with $H_2O$ and the derivatives

(13) $C_5H_8$ was eluted from the new Dowex 50W resin with $NH_4OH$.

were eluted with 0.1 $M$ $NH_4OH$. After a concentration to dryness the residue was extracted with $H_2O$ and the soluble fraction was applied on a 1.4 × 68 cm column of Dowex 50W ($NH_4^+$) resin. The derivatives were eluted with 6 l. of a linear gradient from 0 to 0.15 $M$ $NH_4OH$. Compound **7**, 85 mg, was eluted in fractions 46–71, followed by a mixture of **6**, 57 mg, and 1-(β-aminoethyl-$N$-β-aminoethyl)uracil[14] (**13**), 56 mg, in fractions 114–140, separable by paper chromatography in solvent A. Fractions 180–190 contained 10 mg of 3-(β-aminoethyl-$N$-β-aminoethyl)uracil[14] (**14**), followed by 13 mg of **8** in fractions 242–252. Higher alkylated derivatives were identified in fractions 253–300. Thymine derivatives were eluted in the following fractions: **11**, 120 mg, in 85–110; 1-(β-aminoethyl-$N$-β-aminoethyl)thymine[14] (**15**), 55 mg, in 180–200; **10**, 53 mg, in 206–222, followed by 3-(β-aminoethyl-$N$-β-aminoethyl)thymine[14] (**16**) and by **12**.

(14) Tentatively identified by uv spectra, chromatographic properties, and correct analysis for N.

**Reaction of Alkylated Derivatives with Sodium Hydroxide.**—The alkylated derivatives (10 mg) and 0.2 $N$ NaOH (0.5 ml) were heated at 100° for 10 min. The reaction products were chromatographed on paper and the uv spots were examined.

**Registry No.**—**2**, 66-22-8; **4**, 65-71-4; **5**, 34484-23-6; **6**, 34386-70-4; **6**·HCl, 34386-71-5; **7**, 34386-72-6; **7** HCl, 34386-73-7; **8**·2HCl, 34386-74-8; **9**, 34387-59-2; **10**, 34386-75-9; **10**·HCl, 34386-76-0; **11**, 34386-77-1; **11**·HCl, 34386-78-2; **12**·2HCl, 34386-79-3; ethylenimine, 151-56-4; 2-chloroethylamine, 689-98-5.

# Nucleophilic Substitution at an Acetylenic Carbon. A Mechanistic and Synthetic Study of the Reactions of Phosphines with Haloacetylenes[1]

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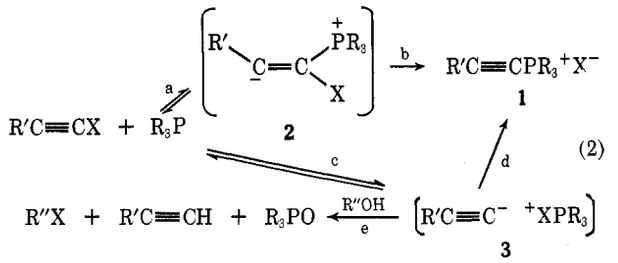
A synthetic route to ethynylphosphonium salts from haloacetylenes, phenylhaloacetylenes, but not alkylhaloacetylenes is described. These salts are electrophiles; when phenylethynyltriphenylphosphonium bromide is treated with tributylphosphine in acetonitrile, the α,β-bis(tributylphosphonium)styrene dibromide is formed. Rate data for the second-order reactions of several systems in DMF are ($\Delta H^{\ddagger}$, kcal/mol; $\Delta S^{\ddagger}$, eu; $k$, $M^{-1}$ $sec^{-1}$ at 36°): $C_6H_5C{\equiv}CBr$–$(C_6H_5)_3P$ (16.8; 23; $8.45 \times 10^{-5}$); $C_6H_5C{\equiv}CCl$–$(C_6H_5)_3P$ (14.5; 29; $1.75 \times 10^{-4}$); $C_6H_5C{\equiv}CBr$–$(n\text{-}C_4H_9)_3P$ (5.4; 44; $2.20 \times 10^{-1}$); $C_6H_5C{\equiv}CCl$–$(n\text{-}C_4H_9)_3P$ (11.5; 27; $5.92 \times 10^{-2}$); $CH_3Br$–$(C_6H_5)_3P$ (11.8; 31; $2.88 \times 10^{-3}$). Both the element effect, $k(Cl) > k(Br)$, and the results of scavenging experiments with methanol provide evidence for mechanistic alternatives. Although tributylphosphine attacks the bromine of phenylbromoacetylene exclusively, attacks on halogen and the terminal carbon atom appear to be competitive in the other systems. The general order of reactivity in substitution at carbon by phosphine nucleophiles is $sp^3 \sim sp > sp^2$.

Nucleophilic displacement at an acetylenic carbon

$$R'C{\equiv}CX + Nuc \longrightarrow R'C{\equiv}C\text{-}Nuc + X \qquad (1)$$

has come of age only within the last few years.[2-7] Substitution attacks on haloalkynes have now been reported for organometallics,[5,7] amines,[2a,e,j,3] phosphites,[2g,3e,6] thiolates,[2b,c,3c] phosphides,[5] alkoxides,[2h,i] etc. Kinetic data in this area are still rare.[2a-c,f-h,j,3e] Our work was undertaken to find out first whether ethynylphosphonium salts could be prepared by process 2, and second to develop a deeper understanding of a still new and relatively unexplored process.



(2)

1a, R′ = R = $C_6H_5$; X = Br
b, R′ = R = $C_6H_5$; X = Cl
c, R′ = $C_6H_5$; R = $n$-$C_4H_9$; X = Br
d, R′ = $C_6H_5$; R = $n$-$C_4H_9$; X = Cl
e, R′ = H; R = $C_6H_5$; X = Cl
f, R′ = H; R = $C_6H_5$; X = Br
g, R′ = H; R = $n$-$C_4H_9$; X = Cl

The first ethynylphosphonium salts were prepared in aprotic solvents.[2b,3d,4] In the presence of a proton donor, the formation of **1** *may* fail, because of diversion of the ion pair **3** along path e. This was found in the system phenylbromoacetylene–triphenylphosphine.[4] For this reason, Hoffmann and Förster suggested that steps c and d in eq 2 were appropriate for this process, and this conclusion has been accepted by workers in the field.[2f] In this paper, we show that all of the options of eq 2 must be retained and describe some of its synthetic applications.

(1) (a) Research supported by National Institutes of Health Grant GM07021. This work was presented in part at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., 1963. (b) Taken from the Ph.D. Thesis of J. I. D., Illinois Institute of Technology, 1970.

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