Studies Concerning the Cyclization of Some 4-Bromoacetylpiperidines to the Corresponding 3-Quinuclidinones[1]

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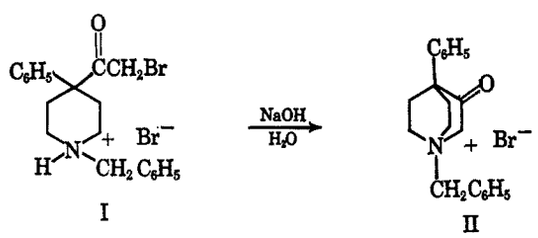
1-Benzyl-4-bromoacetyl-4-phenylpiperidine hydrobromide (I) is converted to 1-benzyl-3-keto-4-phenylquinuclidinium bromide (II) when treated with aqueous sodium hydroxide solution, whereas 4-bromoacetylpiperidine hydrobromide (VI) fails to cyclize to 3-quinuclidinone when neutralized with aqueous sodium hydroxide solution. In order to determine the reason for this difference some other 4-bromoacetylpiperidine hydrobromides were prepared and their reactions with aqueous sodium hydroxide solution were studied. The results obtained are discussed in relation to the conformation of the substituted piperidine rings.

The classical synthesis of quinuclidines involves the intramolecular cyclization of (4-piperidyl)-2-bromo- or -2-iodoethanes.[2-4] With the exception of the conversion of 1-benzyl-4-bromoacetyl-4-phenylpiperidine hydrobromide (I) to 1-benzyl-3-keto-4-phenylquinuclidinium bromide (II) reported by Perrine,[5,5a] the cyclization of 4-bromoacetylpiperidine derivatives has not been studied. In the present paper we describe our

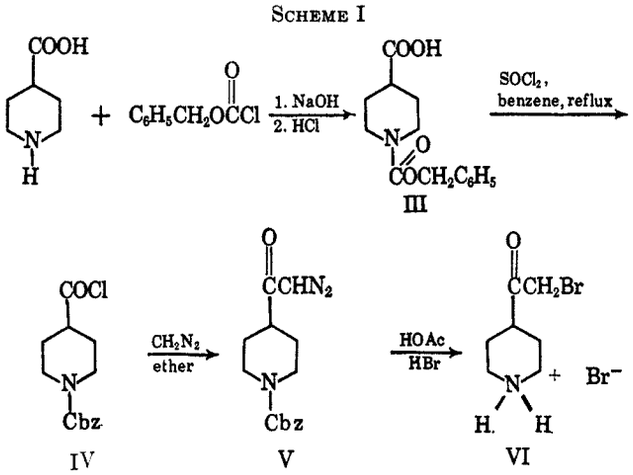


I II

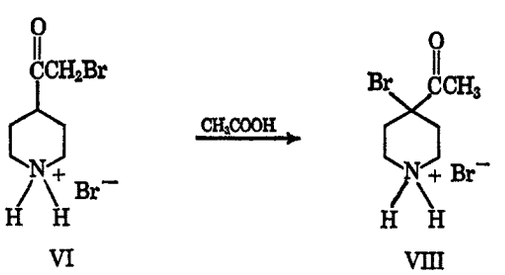
investigation on the cyclization of some 4-bromoacetylpiperidines to the corresponding 3-quinuclidinones.

4-Bromoacetylpiperidine hydrobromide (VI), a possible precursor of 3-quinuclidinone, was prepared by the reactions shown in Scheme I. Isonipecotic acid reacted with carbobenzyloxy chloride to give 1-carbobenzyloxypiperidine-4-carboxylic acid (III). The crude acid was converted by thionyl chloride to the oily acid chloride IV which was characterized as its anilide VII, mp 141.5–142.5°. The reaction of IV with excess diazomethane gave the liquid diazo ketone V. Treatment of V with hydrogen bromide in acetic acid effected both conversion of the diazo ketone group to the bromoacetyl group and decarbobenzyloxylation to give VI in 53% yield from isonipecotic acid. The infrared spectrum of VI showed a band at 1728 cm^{-1} (carbonyl of a bromoacetyl group). The nmr spectrum showed a singlet at δ 4.38 [$-C(=O)CH_2Br$, 1.7 H]. In order to obtain the bromo ketone VI in good yield it was necessary to conduct its preparation at 20° and to avoid excess heating during its recrystallization. Later study disclosed that the lability of this substance at elevated temperature is due to an isomerization reaction. When VI was warmed in glacial acetic acid for 7 days, an isomeric product, mp 154–155°, was obtained in 32% yield. We have formulated this product as 4-acetyl-4-bromopiperidine hydrobromide (VIII) based largely on the nmr spectrum which showed a singlet at δ 2.65 [$CH_3C(=O)-$]. The yield of the isomerization product was increased to 66% and the reaction time reduced to 2 days when the

SCHEME I



III IV V VI



VI VIII

reaction was carried out at 70° in acetic acid saturated with dry hydrogen bromide. This acid-catalyzed isomerization of VI to VIII probably results from the reaction of the protonated ketone with bromide ion to produce an enol that undergoes isomerization and rebromination.[6]

Treatment of VI with 1 equiv of sodium hydroxide followed by immediate extraction into ether gave the free base which reacted rapidly to give an amorphous solid. Analysis of the product by thin layer chromatography[7] showed that no cyclization had occurred. The product appeared to be polymeric and gave a positive 2,4-dinitrophenylhydrazine test. The

(1) This investigation was supported by the Department of the Army and the U. S. Army Edgewood Arsenal Chemical Research and Development Laboratories, Contract No. DA-18-108-AMC-154(A).

(2) H. C. Brown and N. R. Eldred, *J. Am. Chem. Soc.*, **71**, 445 (1949).

(3) C. A. Grob and P. Brennisen, *Helv. Chim. Acta*, **41**, 1184 (1958).

(4) S. Wawzonek, M. F. Nelson, and P. J. Thelen, *J. Am. Chem. Soc.*, **74**, 2894 (1952).

(5) T. D. Perrine, *J. Org. Chem.*, **22**, 1484 (1957).

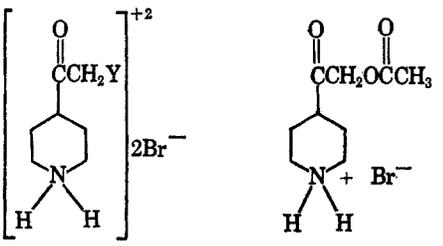
(5a) NOTE ADDED IN PROOF.—Nielsen has recently obtained a 29% yield of 1-benzyl-4-acetoxymethyl-3-ketoquinuclidinium bromide by the cyclization of 1-benzyl-4-acetoxymethyl-4-bromoacetylpiperidine: A. T. Nielsen, *ibid.*, **31**, 1053 (1966).

(6) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 281.

(7) The products were analyzed by thin layer chromatography using microcrystalline cellulose as absorbant. The plates were developed with Dragendorff or 2,4-dinitrophenylhydrazine reagent.

infrared spectrum of the crude product showed a strong carbonyl absorption at 1715 and a weak peak at 1630 cm^{-1}. The 1715-cm^{-1} peak is probably due to ketone products resulting from intermolecular displacement of bromide by the piperidine nitrogen. Repetition of this reaction could lead to polymeric materials. The weak peak at 1630 cm^{-1} may be due to a small amount of amide resulting from an amine-catalyzed Favorskii rearrangement. If VI was treated with 2 equiv of base the product was not extracted into ether. The infrared spectrum of the products in this case was indicative of a carboxylic acid probably resulting from a Favorskii rearrangement.

In contrast to the resistance of VI to undergo intramolecular displacement, we found that intermolecular displacements of the α-bromo ketone took place readily. Treatment of VI with pyridine gave the pyridinium bromide (IX) in 93% yield. The reaction of VI with



IX, Y = –N⁺C₅H₅ 2Br⁻

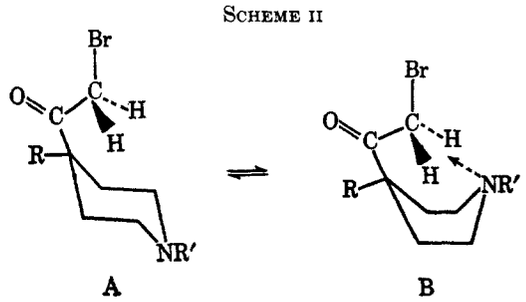
X, Y = –S(CH₃)₂

XI

dimethyl sulfide gave 4-dimethylsulfoniumacetylpiperidine bromide hydrobromide (X) in 60% yield, and treatment of VI with silver acetate gave a 10% yield of the α-acetoxy ketone (XI).

The resistance of 4-bromoacetylpiperidine to undergo cyclization to 3-quinuclidinone contrasts sharply with the facile conversion of 1-benzyl-4-bromoacetyl-4-phenylpiperidine (I) to 1-benzyl-3-keto-4-phenylquinulcidinium bromide (II). These results can be explained in the following way. In order for I or VI to cyclize, the 4-bromoacetyl group and the pair of electrons on nitrogen would have to occupy axial positions in the transition state (see B of Scheme II).

SCHEME II



A ⇌ B

R = H or C_6H_5

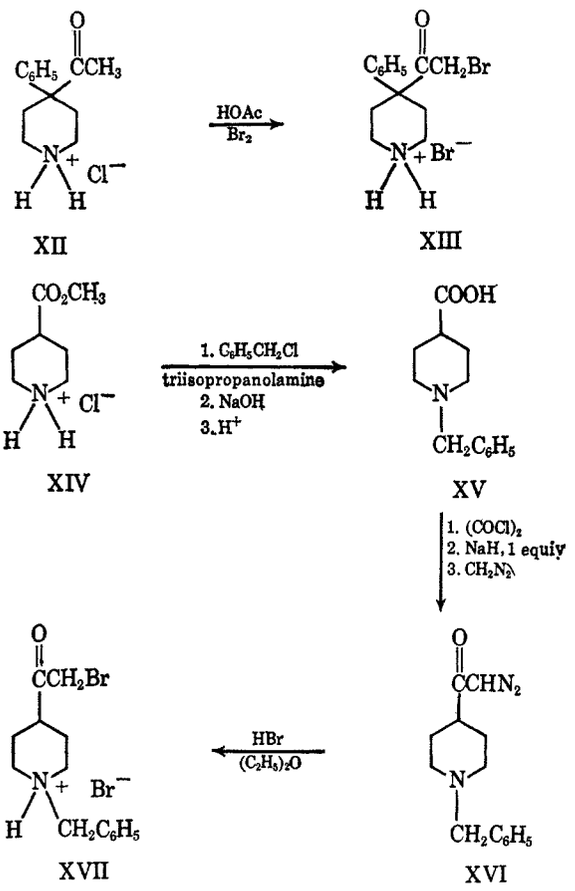
R′ = H or $C_6H_5CH_2$–

Attainment of this reactive conformation is facilitated in the case of ketone I since the phenyl group and the benzyl group[8] in the form B (R = C_6H_5, R′ = $CH_2C_6H_5$) would then be in equatorial positions.

(8) N. L. Allinger, J. G. D. Carpenter, and F. M. Karkowski. [*J. Am. Chem. Soc.*, **87**, 1232 (1965)] have shown by dipole moment studies that the methyl group in N-methylpiperidine prefers the equatorial position by 1.7 kcal/mole, while the hydrogen in piperidine prefers the equatorial position by only 0.4 kcal/mole. These results would tend to indicate that in the ground state and most probably in the transition state the benzyl group in I would occupy the equatorial position to a much greater extent than the hydrogen in VI.

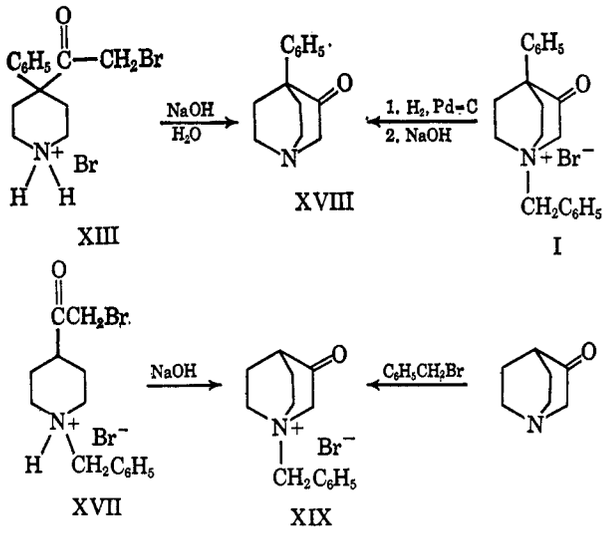
In order to check this explanation experimentally, 4-bromoacetyl-4-phenylpiperidine hydrobromide (XIII) and 1-benzyl-4-bromoacetylpiperidine hydrobromide (XVII) were prepared (Scheme III). The details are given in the Experimental Section.

SCHEME III



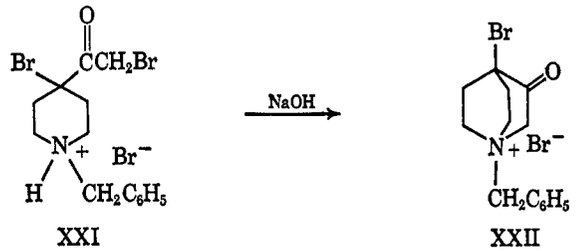
When 4-bromoacetyl-4-phenylpiperidine hydrobromide (XIII) was converted to the free base, 4-phenyl-3-quinuclidinone (XVIII) was obtained in 27% yield while treatment of 1-benzyl-4-acetylpiperidine (XVII) with aqueous sodium hydroxide gave 1-benzyl-3-ketoquinuclidinium bromide (XIX) in 32% yield. The infrared spectra of these cyclization products were identical with the spectra of XVIII and XIX prepared by standard procedures (Scheme IV). It is evident that both the 4-phenyl and 1-benzyl substituents aid the cyclization reaction of 4-bromoacetylpiperidines. We have also prepared 4-bromo-4-bromoacetylpiperidine hydrobromide (XX) by the bromination of either 4-bromoacetylpiperidine hydrobromide (VI) or 4-bromo-4-acetylpiperidine hydrobromide (VIII) and 1-benzyl-4-bromo-4-bromoacetylpiperidine (XXI) by the dibromination of 1-benzyl-4-acetylpiperidine. Treatment of XXI with aqueous sodium hydroxide solution gave 1-benzyl-3-keto-4-bromoquinuclidinium bromide (XXII) in 8% yield whereas treatment of XX with alkaline reagents under conditions similar to those used to cyclize VI and XVII afforded no cyclization products.

SCHEME IV



XIII XVIII I XVII XIX

The failure of XX to undergo a ring closure and the low yield of XXII obtained from XXI may be due to the extreme lability of α,α'-dibromo ketones to alkaline conditions since considerably more decomposition was observed in these reactions than in the cyclization of the monobromo ketones.



XXI XXII

Experimental Section[9]

Preparation of 4-Bromoacetylpiperidine Hydrobromide (VI).—A solution of 12.9 g (0.1 mole) of isonipecotic acid in 25 ml of 4 *N* sodium hydroxide (0.1 mole) was cooled in an ice bath and a total of 30 ml of 4 *N* sodium hydroxide (0.12 mole) and 18.7 g (0.11 mole) of carbobenzyloxy chloride was added alternatively thereto in six equal portions. After stirring for 30 min following the last addition, the reaction mixture was extracted with ether. The aqueous fraction was slowly acidified to congo red end point with 6 *N* hydrochloric acid. An oil separated that was extracted with ethyl acetate. The extracts were dried and the solution was concentrated under vacuum. After drying under vacuum overnight, 23.8 g of 1-carbobenzyloxypiperidine-4-carboxylic acid (III) was obtained as an oil, $\nu_{max}^{CH_2Cl_2}$ 3500–2500 (bonded acid OH), and 1700–1685 cm^{-1} (acid and carbamate carbonyl). The nmr spectrum ($CDCl_3$) showed a singlet at δ = 5.13 (OCH_2-Ar), a singlet at 7.37 (aromatic protons), and a broad peak at 9.80 ppm (CO_2H).

To a solution of the crude 1-carbobenzyloxypiperidine-4-carboxylic acid in 500 ml of benzene (dried by azeotropic distillation) was added 35.70 g (0.3 mole) of freshly distilled thionyl chloride, and the solution was refluxed for 2.5 hr with the system protected from atmospheric moisture by a Drierite drying tube. The reaction mixture was concentrated under reduced pressure (system protected from atmospheric moisture). The resulting oil was redissolved in dry benzene and concentrated to dryness under vacuum twice. The oil was dried under vacuum over sodium hydroxide pellets overnight to give 24.3 g of 1-carbobenzyloxypiperidine-4-carboxylic acid chloride (IV), $\nu_{max}^{CH_2Cl_2}$ 1795 (acid chloride carbonyl), and 1695 cm^{-1} (carbamate carbonyl). The oil was used for the preparation of 1-carbobenzyloxy-4-diazoacetylpiperidine without further purification. The oil was characterized as its anilide VII. Treatment of a portion of the oil prepared in a similar experiment with excess aniline in benzene afforded a 73% yield of the anilide, mp 141.5–142.5°. An analytical sample, prepared by recrystallization from methanol and water, had mp 142-143.2°, $\nu_{max}^{CH_2Cl_2}$ 3285 (NH), 1695 (carbamate carbonyl), and 1655 and 1530 cm^{-1} (amide I and II bands).

Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.56; N, 8.28. Found: C, 71.38; H, 6.42; N, 8.47.

The crude 1-carbobenzyloxypiperidine-4-carboxylic acid chloride in 200 ml of ether was added dropwise to an ice-cooled, well-stirred ethereal solution (500 ml) of diazomethane [0.3–0.4 mole; prepared from 41.2 g (0.4 mole) of N-nitrosomethylurea]. After complete addition the reaction mixture was stirred for an additional 20 min, concentrated to a small volume (50 ml) under vacuum, and redissolved in ether and concentrated again. This was repeated until all the diazomethane was removed. After drying under vacuum overnight 24.2 g of crude 1-carbobenzyloxy-4-diazoacetylpiperidine (V) was obtained as a yellow oil, $\nu_{max}^{CH_2Cl_2}$ 2112 ($N^+{\equiv}N^-$), 1640 (ketone carbonyl adjacent to a diazo group), and 1695 cm^{-1} (carbamate carbonyl).

To a solution of the 1-carbobenzyloxy-4-diazoacetylpiperidine in 50 ml of acetic acid (distilled from potassium permanganate) cooled to 20° was added 99.7 ml (27.9 g, 0.345 mole) of a saturated solution of dry hydrogen bromide in acetic acid. The reaction flask was protected from atmospheric moisture by a Drierite drying tube. The hydrogen bromide addition effected the evolution of nitrogen and carbon dioxide gases. The orange colored reaction mixture was stirred for an additional 30 min at 20°; 500 ml of dry ether was added dropwise to the well-stirred reaction mixture to precipitate the 4-bromoacetylpiperidine hydrobromide as an orange colored solid. After drying, 22.6 g of solid was obtained. The solid was dissolved in methanol, treated with charcoal, and precipitated by the addition of ether to give 15.2 g (52.9% from isonipecotic acid) of 4-bromoacetylpiperidine (VI), mp 153–155°. The analytical sample was prepared by recrystallization from methanol and ether; mp 153–155°; ν_{max}^{KBr} 1728 cm^{-1} (carbonyl of a bromoacetyl group). The nmr spectrum (D_2O) showed a singlet at δ = 4.38 ppm [$C(=O)CH_2Br$, 1.7 H].

Anal. Calcd for $C_7H_{13}Br_2NO$: C, 29.29; H, 4.56; Br, 55.69; N, 4.88. Found: C, 29.46; H, 4.72; Br, 55.46; N, 4.87.

Preparation of 4-Acetyl-4-bromopiperidine Hydrobromide (VIII).—4-Bromoacetylpiperidine hydrobromide (1.15 g, 0.004 mole) was dissolved in acetic acid, heated to 85°, and allowed to remain at this temperature for 7 days. The progress of the reaction was followed by the shift of a carbonyl peak at 1724 in the starting bromo ketone to 1702 cm^{-1} in the product. The reaction mixture was concentrated to dryness by freeze drying. Recrystallization from ethanol and ether afforded 0.368 g (32.2%) of 4-acetyl-4-bromopiperidine hydrobromide (VIII), mp 154–155°. The analytical sample, recrystallized from ethanol and ether had mp 154–155°, ν_{max}^{KBr} 1702 (ketone C=O) and 1360 cm^{-1} [$CH_3(O=)C$]. The nmr spectrum (D_2O) showed a singlet at δ = 2.65 ppm [$CH_3(O=)C$, 3.3 H].

Anal. Calcd for $C_7H_{13}Br_2NO$: C, 29.29; H, 4.56. Found: C, 29.28; H, 4.62.

The yield was increased to 66% and the reaction time reduced to 2 days when the reaction was carried out at 70° in acetic acid saturated with dry hydrogen bromide.

Preparation of 4-(Pyridiniumacetyl)piperidine Bromide Hydrobromide (IX).—4-Bromoacetylpiperidine hydrobromide (0.83 g, 0.003 mole) was suspended in pyridine and allowed to stir at room temperature overnight. Filtration afforded a 93% yield of 4-(pyridiniumacetyl)piperidine bromide hydrobromide (IX), mp 234–236° dec. The analytical sample was prepared by recrystallization from methanol and ether, mp 240–242° (dec), ν_{max}^{KBr} 3490 and 3445 (not assigned), 1732 (ketone C=O adjacent to a $CH_2{}^+NC_5H_5$ group), 1640 and 1494 cm^{-1} (pyridine ring stretching modes). The nmr spectrum (D_2O) showed a multiplet centered at δ = 8.14 (β-pyridine protons, 1.9 H) and a multiplet centered at 8.65 ppm (α- and δ-pyridine protons, 3 H). The

(9) The melting points were obtained on a Kofler hot stage and are corrected. The boiling points are uncorrected. The infrared spectra were obtained using a Perkin-Elmer Model 221 spectrophotometer or Perkin-Elmer 237B grating Infracord. The nmr spectra were obtained using a Varian A-60 spectrometer with samples dissolved in either deuteriochloroform or trifluoroacetic acid (internal standard tetramethylsilane) or deuterium oxide [internal standard 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt]. The gas chromatograms were obtained using a F and M Model 300 gas chromatograph. Microanalyses were by Micro-Tech Laboratories, Skokie, Ill.

protons due to the methylene group between the keto and 1-pyridyl group must be masked by the HDO peak at 4.53 ppm or be acidic enough to exchange with the deuterium oxide.

Anal. Calcd for $C_{12}H_{18}Br_2N_2O$: C, 39.36; H, 4.95; Br, 43.37; N, 7.65. Found: C, 39.27; H, 5.22; Br, 43.22; N, 7.37.

Preparation of 4-Dimethylsulfoniumacetylpiperidine Bromide Hydrobromide (X).—4-Bromoacetylpiperidine hydrobromide (5.74 g, 0.02 mole) was suspended in 25 ml of dimethyl sulfide and allowed to stir overnight. The excess dimethyl sulfide was allowed to evaporate under a stream of nitrogen. Crystallization of the remaining residue gave 4.11 g (60%) of 4-dimethylsulfoniumacetylpiperidine bromide hydrobromide (X), mp 149–153°. The analytical sample prepared by further recrystallization from methanol had mp 151–154°, ν_{max}^{KBr} 2900–2400 (bands typical of amine hydrobromide salt) and 1710 cm^{-1} (ketone carbonyl). The nmr spectrum (D_2O) showed a sharp singlet at δ = 3.0 ppm (CH_3S). The peak due to the methylene protons between the ketone and sulfur must be masked by the HDO peak or be acidic enough to exchange with the deuterium oxide.

Anal. Calcd for $C_9H_{19}Br_2NOS$: C, 30.94; H, 5.50; Br, 45.79; N, 4.01; S, 9.19. Found: C, 31.21; H, 5.49; Br, 46.04; N, 4.14; S, 9.02.

Treatment of 4-Bromoacetylpiperidine Hydrobromide with Silver Acetate.—To a solution of 1.148 g (0.004 mole) of the bromo ketone hydrobromide (VI) in methanol was added 0.668 g (0.004 mole) of silver acetate. After 2 hr the silver bromide was separated by filtration. Concentration of the filtrate afforded 1.15 g of a brown solid, mp 295–310°. Recrystallization from methanol and ether afforded 0.44 g of solid, melting point decomposed over a wide range finally turning completely black at 310°. Attempts to purify the solid were unsuccessful. Addition of more ether to the filtrate afforded 0.102 g (10%) of XI, mp 136.5–139°. The analytical sample was prepared by recrystallization from methanol and ether, mp 137–139°, ν_{max}^{KBr} 2800–2500 (bonds typical of an amine hydrobromide), 1730 (ester carbonyl), 1712 (ketone carbonyl), and 1250 cm^{-1} (CO).

Anal. Calcd for $C_9H_{16}BrNO_2$: C, 40.61; H, 6.06; Br, 30.03; N, 5.26. Found: C, 40.82; H, 6.02; Br, 29.76; N, 5.28.

4-Acetyl-1-benzyl-4-phenylpiperidine Hydrochloride Hydrate.—Using the method of Perrine,[5] 15.67 g (0.05 mole) of 1-benzyl-4-cyano-4-phenylpiperidine hydrochloride yielded 11.15 g, 64%, of 4-acetyl-1-benzyl-4-phenylpiperidine hydrochloride hydrate, mp 240–243°, lit.[5] mp 251–252°, ν_{max}^{KBr} 1712 (C=O).

1-Benzyl-4-bromoacetyl-4-phenylpiperidine Hydrobromide (I).—To a solution of 4.34 g (0.013 mole) of 4-acetyl-1-benzyl-4-phenylpiperidine hydrochloride hydrate in 50 ml of acetic acid (saturated with hydrogen bromide) was added 2.06 g of bromine. After standing at room temperature for 3 days, the mixture was filtered, and ether was added to the filtrate to give 5.45 g (93%) of I, mp 184–191°, lit.[5] mp 200°, ν_{max}^{KBr} 1730 (ketone carbonyl) and 750 and 700 cm^{-1} (aromatic substitution peaks).

1-Benzyl-3-keto-4-phenylquinuclidinium Bromide (II).—Using the procedure reported by Perrine,[5] 1-benzyl-4-bromoacetyl-4-phenylpiperidine hydrobromide (3.47 g, 0.0077 mole) was dissolved in 250 ml of hot water. The solution was subjected to sudden cooling and 100 ml of ether added. To this solution was added 25 ml of 1 *N* sodium hydroxide. The solution was filtered to remove impurities and the ether layer was separated, dried, and concentrated to give an oily solid. Acetone (50 ml) was added to the mixture and left overnight. Filtration gave 2.0 g (71%) of 1-benzyl-3-keto-4-phenylquinuclidinium bromide (II), mp 275–280°; lit.[5] mp 290–295°; ν_{max}^{KBr} 1755 (ketone C=O adjacent to $CH_2{}^+N<$), 1502 (aromatic stretching modes), and 702 cm^{-1} (aromatic substitution peaks). The nmr spectrum (CF_3COOH) showed a broad singlet at δ = 4.46 [$C(=O)CH_2{}^+N<$ 1.8 H], a broad singlet at 4.63 ($ArCH_2{}^+N<$, 2.0 H), a multiplet centered at 7.33 ($C_6H_5C<$, 5.2 H), and a singlet at 7.63 ppm (aromatic protons of the benzyl group, 5.2 H).

4-Acetyl-4-phenylpiperidine Hydrochloride (XII).—Using the method of Perrine,[5] a solution of 4.01 g (0.011 mole) of 4-acetyl-1-benzyl-4-phenylpiperidine hydrochloride hydrate in 40 ml of methanol and 9 ml of water containing 1 ml of 2.5 *N* hydrochloric acid and 2 g of 10% palladium–carbon catalyst was hydrogenated in the Parr hydrogenator until hydrogen ceased to be taken up. The catalyst was separated by filtration. Concentration of the filtrate afforded 2.05 g (78%) of 4-acetyl-4-phenylpiperidine hydrochloride (XII), mp 238–241°; lit.[5] mp 245°; ν_{max}^{KBr} 1712 cm^{-1} (ketone C=O). The nmr spectrum (D_2O) showed a singlet at δ = 2.17 [$CH_3(=O)C$, 3.2 H], and a singlet at 7.21 ppm (aromatic protons, 5.0 H).

4-Bromoacetyl-4-phenylpiperidine Hydrobromide (XIII).—To a solution of 3.39 g (0.014 mole) or 4-acetyl-4-phenylpiperidine hydrochloride in 100 ml of acetic acid (saturated with hydrogen bromide) was added 0.95 ml of bromine. The mixture was stirred overnight at room temperature. The resultant yellow solution was filtered. More product was obtained by the addition of ether to the filtrate; total yield of 4-bromoacetyl-4-phenylpiperidine hydrobromide (XIII) was 4.40 g (87%), mp 202–206°, ν_{max}^{KBr} 1725 cm^{-1} (ketone carbonyl of a bromoacetyl group). The nmr spectrum (D_2O) showed a singlet at δ = 4.29 [$C(=O)CH_2Br$, 1.7 H] and a singlet at 7.55 ppm (aromatic protons, 5.2 H).

Anal. Calcd for $C_{13}H_{17}Br_2NO$: C, 43.00; H, 4.72; N, 3.86. Found: C, 42.70; H, 4.69; N, 3.94.

If the bromination was carried out in acetic acid not saturated with dry hydrogen bromide, nonreproducible results were obtained. In some experiments bromination of XII to XIII occurred smoothly but in others no bromination or only partial bromination was obtained.

Preparation of 4-Phenyl-3-quinuclidinone (XVIII) from 1-Benzyl-3-keto-4-phenylquinuclidinium Bromide (II).—A solution of 1.54 g (0.0055 mole) of 1-benzyl-3-keto-4-phenylquinudinium bromide in 35 ml of methanol and 25 ml of water containing 0.50 g of 10% palladium–carbon catalyst was hydrogenated in a Parr hydrogenator until hydrogen ceased to be taken up. The catalyst was separated by filtration. Concentration of the filtrate afforded 1.05 g (91%) of crude 4-phenyl-3-quinuclidinone hydrobromide; mp 276–279°; lit.[5] mp 285–287°; ν_{max}^{KBr} 2900–2400 (typical amine hydrobromide absorption), and 1755 cm^{-1} (ketone C=O). Treatment of the hydrobromide with dilute sodium hydroxide gave the free base, 4-phenyl-3-quinuclidinone, mp 149–153°. The analytical sample prepared by recrystallization from cyclohexane had mp 155–157°; reported mp 157–158°. The infrared spectrum showed absorption at 3025, 3065, 3085 (aromatic CH) 2970–2860 (a number of CH peaks), 1735 (C=O), 1605, 1510 (aromatic stretching modes), and 770 and 700 cm^{-1} (aromatic substitution peaks). The nmr spectrum ($CDCl_3$) showed a multiplet at δ = 2.0–2.5 $\left(>C<\begin{matrix}CH_2^-\\CH_2^-\end{matrix}\right)$, a multiplet at 2.93–3.33 $\left(\begin{matrix}CH_2\\CH_2\end{matrix}>{}^+N<\right)$, a singlet (broad) at 3.4 [$CH_2(=O)C$], and a doublet at 7.28 ppm (aromatic protons).

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.42; H, 7.62; N, 6.95.

The Preparation of 4-Phenyl-3-quinuclidinone (XVIII) from 4-Bromoacetyl-4-phenylpiperidine Hydrobromide (XIII).—4-Bromoacetyl-4-phenylpiperidine hydrobromide (0.5112 g, 0.00213 mole) was dissolved in 10 ml of water by warming on a steam bath. The solution was made basic with potassium hydroxide pellets and heated on the steam bath until precipitation ceased. Filtration afforded 0.113 g (27%) of 4-phenyl-3-quinuclidinone (XVI), mp 148–153°. The infrared and nmr spectra of this product were identical with 4-phenyl-3-quinuclidinone prepared from 1-benzyl-3-keto-4-phenylquinuclidinium bromide.

Preparation of Piperidine-4-carboxylic Acid Methyl Ester Hydrochloride (XIV).—A stream of dry hydrogen chloride gas was passed through a suspension of 10 g of piperidine-4-carboxylic acid in methanol at room temperature until all the solid dissolved. The solution was cooled in an ice bath and treatment continued until the solution was saturated. After standing 4 hr at room temperature, volatiles were removed under reduced pressure, and the remaining solid was washed with ether and dried under vacuum over sodium hydroxide pellets. A 93% yield of XIV was obtained, mp 157–160°. The analytical sample was prepared by recrystallization from methanol and ether, mp 161–164°; ν_{max}^{KBr} 1730 cm^{-1} (ester (C=O)).

Anal. Calcd for $C_7H_{14}ClNO_2$: C, 46.80; H, 7.85. Found: C, 46.49; H, 7.87.

Preparation of the Methyl Ester of 1-Benzylpiperidine-4-carboxylic Acid.—To a sample of methyl isonipecotate hydrochloride (42.1 g, 0.234 mole) suspended in 300 ml of methylene chloride was added 29.62 g (0.234 mole) of benzyl chloride. To this mixture was added dropwise 109.21 g (0.468 mole) of triisopropanolamine in 250 ml of methylene chloride. The mixture was allowed to stir at room temperature overnight. The solution was concentrated, taken up in ether, and washed with water. Concentration of the dried ether layer gave 48 g of a liquid. Distillation under reduced pressure gave 28.6 g (52%) of the methyl ester of 1-benzylpiperidine-4-carboxylic acid, bp 115°

(0.3 mm); $n^{25}D$ 1.5049; lit.[10] bp 190–192° (21 mm); $n^{24}D$ 1.5177; ν_{max}^{KBr} 1735 cm^{-1} (C=O).

Preparation of 1-Benzylpiperidine-4-carboxylic Acid (XV).—To a solution of 28.5 g (0.12 mole) of the methyl ester of 1-benzylpiperidine-4-carboxylic acid in a mixture of 360 ml of dioxane (distilled from sodium) and 150 ml of water was added 122 ml of 1 *N* sodium hydroxide. The mixture was stirred for 20 hr then 122 ml of 1 *N* hydrochloric acid was added. The solution was concentrated by freeze drying to give a white solid which was extracted with hot isopropyl alcohol. The isopropyl alcohol extracts were concentrated to a small volume and cooled to give 19.2 g (72%) of 1-benzylpiperidine-4-carboxylic acid; mp 168–170°. The analytical sample was prepared by recrystallization from the same solvent, mp 169–170.5°. ν_{max}^{KBr} 3700–3200 (carboxylic acid OH), 3080 and 3045 (aromatic CH), and 1617 cm^{-1} (amino acid carbonyl). The nmr spectrum showed a singlet at δ = 3.87 ($ArCH_2N<$, 2.1 H), a singlet at 7.35 (aromatic protons, 5 H), and a singlet at 10.6 ppm [C(=O)OH, 0.94 H].

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.88; N, 6.39. Found: C, 70.76; H, 7.83; N, 6.30.

Preparation of 1-Benzyl-4-bromoacetylpiperidine Hydrobromide (XVII).—A mixture of 7 g (0.032 mole) of 1-benzylpiperidine-4-carboxylic acid and 15 ml of oxalyl chloride was refluxed together for 2 hr. The excess oxalyl chloride was removed on a rotary evaporator and the residue dried to constant weight under high vacuum to give 8.15 (100%) of crude 1-benzylpiperidine-4-carboxylic acid chloride; $\nu_{max}^{CH_2Cl_2}$ 1790 cm^{-1} [C(=O)Cl]. The crude acid chloride was dissolved in 250 ml of dry tetrahydrofuran and stirred with 0.91 g (0.038 mole) of sodium hydride for 2 hr. The sodium chloride and excess sodium hydride were separated from the solution by filtration under nitrogen. The filtrate was then added dropwise to an excess of diazomethane in ether. After the addition was completed, the reaction mixture was concentrated on a rotary evaporator to give 6.16 g of a dark oil. Chromatography of this oil on Florisil afforded 2.16 g (28%) of 1-benzyl-4-diazoacetylpiperidine (XVI) as a yellow liquid; $\nu_{max}^{CH_2Cl_2}$ 2110 ($^+N{\equiv}N^-$) and 1640 cm^{-1} (C=O). The nmr spectrum ($CDCl_3$) showed a singlet at δ = 5.47 ppm [C(=O)CHN_2, 1 H]. This liquid was used without further purification to prepare XVII.

To an ice cooled solution of 2.16 g of XVI in 50 ml of ether was added an ethereal solution of hydrogen bromide until precipitation was completed. The solid was separated and recrystallized from an ethanol and ether mixture to give 2.35 g (71%) of 1-benzyl-4-bromoacetylpiperidine hydrobromide (XVII); mp 157.5–159.5°; ν_{max}^{KBr} 1725 cm^{-1} (C=O). The nmr spectrum (CF_3COOH) showed a singlet at δ = 4.2 ($ArCH_2$) and a broad doublet at 4.47 ppm [C(=O)CH_2Br].

Anal. Calcd for $C_{14}H_{19}Br_2NO$: C, 44.58; H, 5.08; Br, 42.38; N, 3.71. Found: C, 44.91; H, 5.26; Br, 42.42; N, 3.98.

Preparation of 1-Benzyl-3-ketoquinuclidinium Bromide (XIX) from 3-Quinuclidinone.—3-Quinuclidinone (0.375 g, 0.003 mole) was added to a solution of 0.7 ml of benzyl bromide in 10 ml of benzene. After stirring at room temperature for 5 hr, the solid that formed was filtered and dried to give 0.735 g (83%) of 1-benzyl-3-ketoquinuclidinium bromide (XIX), mp 230–234°. Recrystallization from a methanol and ethyl acetate mixture gave the analytical sample; mp 233–236°; ν_{max}^{KBr} 1750 cm^{-1} (ketone carbonyl adjacent to $CH_2{}^+N<$ group).

Anal. Calcd for $C_{14}H_{18}BrNO$: C, 56.76; H, 6.12; N, 4.73. Found: C, 56.58; H, 5.97; N, 4.66.

Preparation of 1-Benzyl-3-ketoquinuclidinium Bromide (XIX) from 1-Benzyl-4-bromoacetylpiperidine Hydrobromide XVII.—A stirred mixture of 0.301 g (0.8 mmole) of 1-benzyl-4-bromoacetylpiperidine hydrobromide, 5 ml of water, and 15 ml of ether was cooled in an ice bath and 1 ml of 1 *N* sodium hydroxide solution was added. The ether layer was separated and the aqueous layer was extracted twice more with 10-ml portions of ether. The combined ether layers were dried over anhydrous sodium sulfate, concentrated under a stream of nitrogen and 5 ml of acetone was added to the residue. After standing at room temperature overnight, 0.767 g (32%) of 1-benzyl-3-ketoquinuclidinium bromide was formed, mp 226–230°. The infrared spectrum of this product was identical with the spectra of XIX obtained from treatment of 3-quinuclidinone with benzyl bromide.

Preparation of 4-Bromo-4-bromoacetylpiperidine Hydrobromide (XX) from 4-Bromoacetylpiperidine Hydrobromide (VI).—To a solution of 1.43 g (0.005 mole) of 4-bromoacetylpiperidine hydrobromide in 15 ml of acetic acid saturated with hydrogen bromide was added 0.080 g (0.005 mole) of bromine in 5 ml of acetic acid. The bromine was taken up immediately. The hydrogen bromide was expelled by passing nitrogen through the solution. Recrystallization of the solid obtained from a methanol and ether mixture gave 0.95 g (52%) of 4-bromo-4-bromoacetylpiperidine hydrobromide, mp 151–153° (dec). The analytical sample was prepared by recrystallization from methanol, mp 156–158° dec; ν_{max}^{KBr} 1726 cm^{-1} (C=O). The nmr spectrum (D_2O) showed a singlet at δ = 4.71 ppm [C(=O)CH_2Br, 1.9 H].

Anal. Calcd for $C_7H_{12}Br_3NO$: C, 22.97; H, 3.31; Br, 65.52; N, 3.83. Found: C, 23.12; H, 3.37; Br, 65.37; N, 3.98.

Preparation of 4-Bromo-4-bromoacetylpiperidine Hydrobromide (XX) from 4-Acetyl-4-bromopiperidine Hydrobromide (VIII).—To a solution of 0.574 g (0.002 mole) of 4-acetyl-4-bromopiperidine hydrobromide in 25 ml of acetic acid saturated with dry hydrogen bromide was added 0.31 g (0.002 mole) of bromine in 3.2 ml of acetic acid. The bromine was taken up immediately. The excess hydrogen bromide was expelled by passing nitrogen through the solution. The solution was concentrated by freeze drying to give an orange solid. Recrystallization from methanol gave 0.3 g (42%) of 4-bromo-4-bromoacetylpiperidine hydrobromide, mp 153–153.5°. The infrared spectrum of the compound was identical with a sample prepared from 4-bromoacetylpiperidine hydrobromide.

Preparation of 1-Benzyl-4-acetylpiperidine.—1-Benzyl-4-acetylpiperidine was prepared according to the procedure reported by Nielsen, *et al.*;[11] bp 123° (0.04 mm); $n^{25}D$ 1.5287; lit.[11] bp 124° (0.4 mm); $n^{25}D$ 1.5276.

The hydrobromide was recrystallized from ethanol, mp 147–149°; ν_{max}^{KBr} 1702 cm^{-1} (C=O). The nmr spectrum (D_2O) showed a sharp singlet at δ = 2.30 (CH_3CO), a singlet at 4.38 (CH_2Ar), and a singlet at 7.6 ppm (aromatic protons).

Anal. Calcd for $C_{14}H_{20}BrNO$: C, 56.38; H, 6.76; N, 4.70. Found: C, 56.39; H, 6.82; N, 4.83.

Preparation of 1-Benzyl-4-bromo-4-bromoacetylpiperidine Hydrobromide (XXI).—To a stirred solution of 0.596 g (0.002 mole) of 1-benzyl-4-acetylpiperidine hydrobromide in 10 ml of acetic acid was added dropwise 0.640 g of bromine in 5 ml of acetic acid while dry hydrogen bromide was passed through the solution. After the addition was completed, the hydrogen bromide flow was stopped; the solution was allowed to stir for 1 hr. Nitrogen was passed through the solution until hydrogen bromide ceased to be displaced. Separation of the solid which separated plus the solid obtained upon dilution of the filtrate with ether afforded 0.790 g (87%) of 1-benzyl-4-bromo-4-bromoacetylpiperidine hydrobromide (XXI), mp 161–162°. Recrystallization of the solid from methanol afforded the analytical sample; mp 164–165°; ν_{max}^{KBr} 1730 cm^{-1} (C=O). The nmr spectrum showed a singlet at δ = 4.58 with a shoulder at 4.50 ppm [$ArCH_2$ and C(=O)CH_2Br].

Anal. Calcd for $C_{14}H_{18}Br_3NO$: C, 36.87; H. 3.98; Br, 52.57; N, 3.07. Found: C, 37.32; H, 4.15; Br, 52.33; N, 3.39.

Preparation of 1-Benzyl-3-keto-4-bromoquinuclidinium Bromide (XXII).—1-Benzyl-4-bromo-4-bromoacetylpiperidine hydrobromide (2.28 g, 0.005 mole) was treated with 1 *N* sodium hydroxide solution under the same conditions used to prepare 1-benzyl-3-ketoquinuclidinium bromide (XIX) from 1-benzyl-4-bromoacetylpiperidine hydrobromide (XVII). The crude product obtained (0.51 g) was dissolved in 20 ml of water saturated with butanol and purified on a countercurrent apparatus using a butanol and water system. The distribution was terminated after 40 transfers. The product was isolated from tubes 4 to 13. Recrystallization of the solid from methanol afforded 0.15 g (8%) of 1-benzyl-3-keto-4-bromoquinuclidinium bromide, mp 253–255° dec; ν_{max}^{KBr} 1765 cm^{-1} (C=O).

Anal. Calcd for $C_{14}H_{17}Br_2NO$: C, 44.89; H, 4.56. Found: C, 44.82; H, 4.75.

1-Benzyl-4-bromo-4-bromoacetylpiperidine hydrobromide (0.25 g) was isolated from tubes 14 to 25, mp 163–165°. An infrared spectrum of this product was identical with the spectrum of an authentic sample. This product must have formed from the reaction of 1-benzyl-4-bromo-4-bromoacetylpiperidine with hydrogen bromide. The hydrogen bromide was apparently formed

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as a result of the decomposition of part of the 1-benzyl-4-bromo-4-bromoacetylpiperidine.

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Ring-Opening Reactions of P-1-Aziridinyl-N,N,N′,N′-tetramethylphosphonic Diamides

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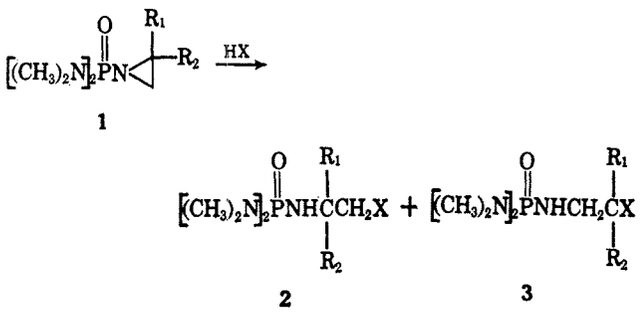
Ring-opening reactions of the aziridine rings of P-1-aziridinyl- (**1a**), P-(2-methyl-1-aziridinyl)- (**1b**), and P-(2,2-dimethyl-1-aziridinyl)-N,N,N′,N′-tetramethylphosphonic diamide (**1c**) are described. For those reactions in which mixtures of ring-opened isomers were produced, an estimate of the composition was made from the proton nmr spectra of the mixtures. Reactions of **1b** with acidic reagents gave mostly the products of direct attack upon the aziridine ring, whereas **1c** yielded mainly products formally derived from a tertiary carbonium ion. Three of the addition products prepared exhibited magnetically nonequivalent dimethylamino groups.

In our studies of the structure–activity relationships in insect chemosterilants, we observed that the sterilizing activity of aziridinylphosphine oxides was inversely related to the degree of substitution on the aziridine ring carbons.[1] Because the process of ring cleavage is considered to be a necessary step in the physiologically important reaction of aziridine-containing sterilants, and because the direction of cleavage of such ring-substituted aziridines had not been studied chemically to any great extent,[2] we investigated ring-opening reactions of P-1-aziridinyl- (**1a**), P-(2-methyl-1-aziridinyl)- (**1b**), and P-(2,2-dimethyl-1-aziridinyl)-N,N,N′,N′-tetramethylphosphonic diamide (**1c**). The structures of the products were confirmed by chemical analyses, and proton nmr and infrared spectra. For reactions in which a mixture of two possible open-chain isomers was produced, an estimate of the product composition was made from the nmr data. The generalized equation for the additions is shown in Scheme I; the physical properties and chemical analyses of the products are summarized in Table I.

SCHEME I



1–3a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = R_2 = CH_3$

The C-unsubstituted aziridine (**1a**) reacted with pyridine hydrochloride in chloroform to give, in high yield, **2a** (X = Cl) which polymerized on attempted distillation; the resulting viscous liquid cooled to a glass. Reactions of 1a with thiophenol in carbon tetrachloride, with pyrrolidine, and with methanol containing sodium methoxide also produced high yields of the corresponding adducts. Compounds **2a** (X = 1-pyrrolidinyl) and **2a** (X = OCH_3) were distillable liquids but **2a** (X = phenylthio) decomposed on attempted distillation. Correct chemical analyses were obtained for each of these products and their infrared spectra in carbon tetrachloride solution exhibited absorptions at 3150–3300 cm^{-1} ascribed to NH stretching.

Reaction of **1a** with *p*-nitrobenzoic acid in chloroform produced a complex of *p*-nitrobenzoic acid with the adduct **2a** (X = *p*-nitrobenzoyloxy). Compound **2a** itself was obtained by treatment of the complex with aqueous sodium carbonate. Acidification of the carbonate solution produced an equivalent of *p*-nitrobenzoic acid. The proton nmr spectra of these adducts are listed in Table II. The NH nmr absorption for these compounds would be expected to be concentration dependent because of hydrogen bonding with the oxygen atom bound to phosphorus. Conceivably there might also be hydrogen bonding with the substituent X. The NH absorption for **2b** (X = *p*-nitrobenzoyloxy) was obscured by the N-methyl absorptions when the concentration was 20%. At a 40% concentration the NH appeared as a multiplet centered at τ 6.8 clear of the N-methyl absorptions and to the low-field side of them; at a 5% concentration the NH absorption had moved clear and to the high-field side of the N-methyl absorptions at τ 7.8. Upon addition of D_2O the absorption ascribed to NH disappeared. In the nmr spectra of the various adducts the amidic proton absorption is expected to be in the region of τ 6.8–7.8. The two methylene absorptions of **2a** (X = *p*-nitrobenzoyloxy) can therefore be identified. The methylene group adjacent to oxygen appeared as the expected triplet centered at τ 5.61, whereas the other was a complex multiplet at 5.8–6.9 containing the amidic proton absorption.

The reaction of P-(2-methyl-1-aziridinyl)-N,N,N′,N′-tetramethylphosphonic diamide (**1b**) with pyridine

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