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Synthesis and Reactions of Some Tetrahydroquinolizinium Salts. Possible Precursors to Cycl[3.3.3]azine

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Several 6-methyl-4-substituted 1,2,3,4-tetrahydroquinolizinium salts have been prepared from suitably substituted 2-picolines. As these compounds are potential intermediates in the synthesis of cycl[3.3.3]azine, several pertinent reactions were studied with this objective in mind. All attempts, however, were unsuccessful and reasons for the failures are discussed.

The nitrogen heterocycle **1**, given the trivial names cycl[3.3.3]-azine[1] and tricyclazine,[2] is of considerable

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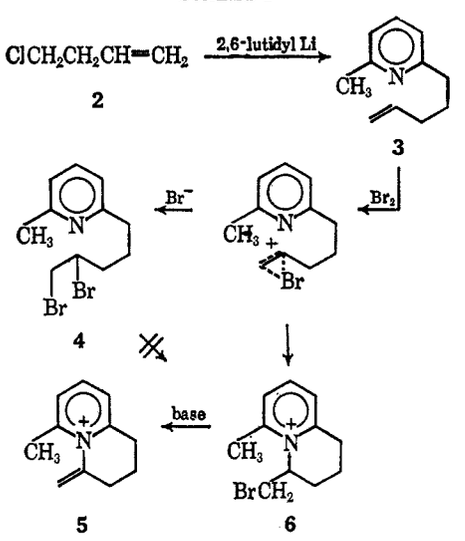
theoretical interest,[1,3] and has been the subject of much synthetic study.[2,4-8] We now report some of our work on 1,2,3,4-tetrahydroquinolizinium salts which are potential precursors of compound **1**.

A. The Pentenylpicoline[9] Route.—Pentenylpicoline **3** was prepared in two ways, 1-chlorobut-3-ene[10] (**2**) (see Scheme I), on reaction with 2,6-lutidyllithium, gave the same product **3**, as was obtained from the reaction of 1-bromopent-4-enyllithium[11] with 2-picoline.

Treatment of **3** with bromine resulted in the formation of two products **4** and **6**. Compound **4** was a high boiling oil, whereas **6** was an isomeric white salt probably formed by simultaneous bromination and cyclization of the olefin. Compound **4** could not be converted into **6** under the reaction conditions, nor could any conditions be found for this transformation.

SCHEME I



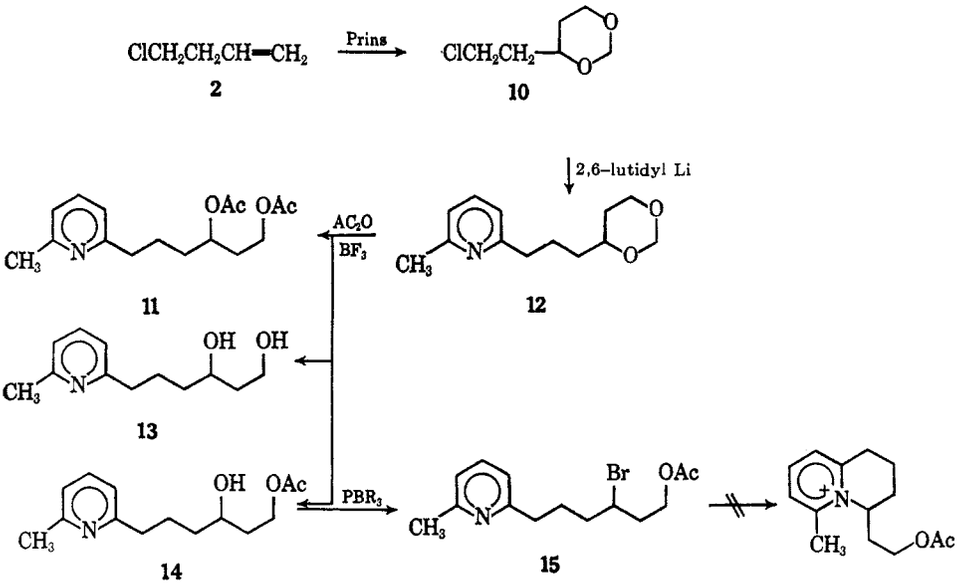
Treatment of the salt **6** with aqueous sodium cyanide yielded a salt which was isolated as the perchlorate, and which from spectral evidence appeared to have no nitrile group. Nmr evidence suggested that the new salt was the dehydrobromination product, 6-methyl-4-methylene-1,2,3,4-tetrahydroquinolizinium (**5**) perchlorate which could also be obtained when sodium carbonate was used instead of sodium cyanide.

In retrospect, it is not surprising that the observed elimination occurred as the bromine atom which was to be displaced would be directed away from the methyl group in the 6 position thus being effectively shielded against nucleophilic displacement by cyanide, and also, the hydrogen in the 4 position is expected to be relatively acidic as it is α to a positively charged nitrogen.

The reaction of the salt **6** with base or cyanide ion could be conveniently followed by nmr and some

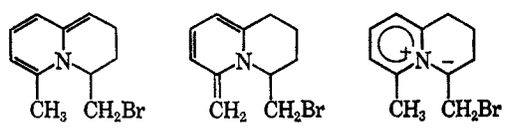
(1) R. J. Windgassen, Jr., W. W. Saunders, Jr., and V. Boekelheide, *J. Amer. Chem. Soc.*, **81**, 1459 (1959).
(2) V. Boekelheide and W. G. Gall, *J. Org. Chem.*, **19**, 499 (1954).
(3) R. D. Brown and B. A. W. Coller, *Mol. Phys.*, **2**, 158 (1959).
(4) H. V. Hansen and E. D. Amstutz, *J. Org. Chem.*, **28**, 393 (1963).
(5) I. Murskoshi, A. Kubo, J. Saito, and J. Haginina, *Chem. Pharm. Bull.* (Tokyo), **12**, 747 (1964).
(6) V. Boekelheide, H. Fritz, J. M. Ross, and H. X. Kaempfen, *Tetrahedron*, **20**, 33 (1964).
(7) W. K. Gibson and D. Leaver, *Chem. Commun.*, **1**, 11 (1965).
(8) D. Leaver and J. D. R. Vass, *J. Chem. Soc.*, 1629 (1965).
(9) The term pentenylpicoline, used throughout this text, should be taken to mean 1-[2-(6-methylpyridyl)]-pent-4-ene (**3**).
(10) J. D. Roberts and R. H. Mazur, *J. Amer. Chem. Soc.*, **73**, 2509 (1952).
(11) Prepared by standard methods[12-14] from tetrahydrofurfuryl alcohol.
(12) I. A. Brooks and H. R. Snyder, *Org. Syn.*, **25**, 84 (1945).
(13) F. B. LaForge, N. Green, and W. A. Gersdorff, *J. Amer. Chem. Soc.*, **70**, 3707 (1948).
(14) H. Gilman, F. W. Moore, and O. Baine, *ibid.*, **63**, 2479 (1941).

SCHEME II



interesting observations were made. The salt was dissolved in deuterium oxide and its nmr spectrum was measured. Anhydrous potassium carbonate was added and the spectra were observed at intervals. The first observation was that the triplet centered at τ 6.7 quickly disappeared, suggesting that the hydrogens in the 1 position were undergoing base-catalyzed exchange with the solvent; next, the singlet at τ 7.13 disappeared suggesting that deuteration of the 6-methyl group was occurring; and, finally, the broad absorption at τ *ca.* 4.7 and the doublet at 6.14 (J = 8 Hz) both disappeared at the same rate to give way to another pair of absorptions at 4.22 and 4.60.

The order of the acidities (1 proton > methyl proton > 4 proton) can be understood by a consideration of the stability of the three conjugate bases **7**–**9** which



7 8 9

would be the major contributing forms to the respective bases. Structure **9** in which there must always be charge separation would be least stable while steric effects would account for the relative stabilities of **7** and **8**.

The greater ease of removal of a proton from the 1 position in **6** than from the 6-methyl group may be of importance in later attempts to form the third ring in the cyclazine skeleton and may lead to an unwanted azabicyclo[2.2.2]octane. It is also of interest that **8** did not cyclize to a hexahydrocycl[3.3.2]azine.

B. The 1,3-Dioxane Route.—The above route failed in the attempt to add the final carbon atom to the bicyclic system. To overcome this difficulty a method was investigated whereby sufficient carbon atoms were incorporated into the system prior to cyclization. The acidity of the 2-methyl protons in substituted pyridines and of 6-methyl protons in quinolizinium salts make 2,6-lutidine an attractive starting point in any such synthesis. A conveniently protected substrate was considered to be 4-(2-chloroethyl)-1,3-dioxane which was readily prepared from 1-chlorobut-3-ene by a modification of the Prins reaction.[15] By performing the acid-catalyzed addition of formaldehyde to the olefin **2** in ether, the yield of the major by-product, 5-chloropentane-1,3-diol, could be kept to a minimum. The product **10** reacted smoothly with 2,6-lutidyllithium to yield **12** (Scheme II), the structure of which was substantiated by spectral data.

Cleavage of the metadioxane ring in **12** was most conveniently accomplished by the mild method of Youssefyeh and Mazur[16] which not only provided an effective procedure for the metadioxane ring opening, but partial hydrolysis of the diacetate produced gave as the major product the hydroxyacetate **14**, in which the primary hydroxyl was protected against further reaction in the next step. Chromatographic separation of the reaction products also gave **11** (15%) and the diol **13** (5%). Treatment of **13** or **14** with acetic anhydride also gave the diacetate **11**.

The hydroxyacetate **14** was treated with phosphorus tribromide to give a small yield of the corresponding bromide **15** which could be reconverted into **14** by hydrolysis in aqueous dioxane containing silver perchlorate. All attempts to cause the bromide **15** to cyclize were to no avail and this route was thus abandoned.[17]

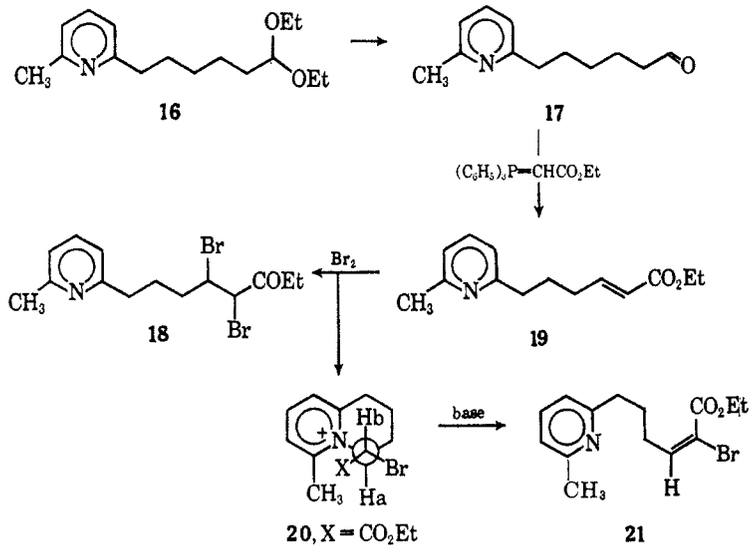
C. The α,β-Unsaturated Ester Route.—As is evident from the two approaches discussed, the displacement of a side-chain bromine atom by the nitrogen of a 2,6-disubstituted pyridine is not a practicable approach to the tetrahydroquinolizinium nucleus. However, the reaction of pentenylpicoline with bromine has shown that cyclization during bromination of a suitably situated double bond is certainly feasible and the accessibility of olefins *via* the Wittig reaction made this appear a most attractive route.

(15) H. J. Prins, *Proc. Acad. Sci.* (Amsterdam), **22**, 51 (1919).

(16) R. D. Youssefyeh and Y. Mazur, *Tetrahedron Lett.*, **26**, 1287 (1962).

(17) Two objections could have been raised against this method: (a) in view of the failure of **4** to cyclize, **15** might have been expected to behave similarly; and (b) the relative acidities of the methyl and methylene protons in **6** leave the mode of closure of the third ring open to speculation. In anticipation of these objections it is pointed out that this route was started well before the above results became known.

SCHEME III



β-Chloropropionaldehyde acetal[18] was treated with 2,6-lutidyllithium to yield the acetal **16** which upon hydrolysis gave the aldehyde **17** (Scheme III).

Of the Wittig reagents suitable for condensation with aldehyde **17**, that derived from ethyl bromoacetate was considered most desirable, particularly in view of ease with which it could be prepared.[19]

On reaction of the phosphorane with the aldehyde **17** a product was obtained which showed ultraviolet and infrared absorptions and an nmr spectrum compatible with the *trans* α,β-unsaturated ester **19** expected from the Wittig reaction.

Treatment of **19** with bromine in aqueous dioxane gave two products, a high boiling oil, tentatively assigned the structure **18** on the basis of its mass spectrum and method of preparation, and a white salt which was assigned the structure **20**.

When **20** was treated with base, closure of the third ring did *not* occur but instead, the sole product isolated in good yield was **21**. It was of interest to obtain a qualitative estimate of the relative rates of proton removal from the 4-methyl group and the position α to the ester, as cyclization of **20** to a tricyclic nucleus would require that the former reaction should occur at a measurable rate. The reaction in deuterium oxide was studied by nmr and the only detectable reaction was that yielding **21**, there being a complete absence of deuterium exchange at the 4-methyl group.

Experimental Section[20]

The Reaction between 2,6-Lutidyllithium and 1-Chlorobut-3-ene.—The preparation of 2,6-lutidyllithium is a modification of the method reported[21] for 2-picolyllithium, and its reaction with the butenyl chloride is based upon the reaction[22] of 2-picolyllithium with isopropyl bromide. A freshly prepared solution of phenyllithium was added dropwise to a solution of 2,6-lutidine (25 ml) in ether (100 ml), and stirred for 1 hr. Chlorobutene (10 g) in ether (50 ml) was added slowly and the mixture was then heated under gentle reflux for 5 hr, cooled, and poured onto ice. The ether phase was separated and the aqueous phase was further extracted with ether. The bases were extracted into 1 *M* aqueous hydrochloric acid. The acid solution was basified with potassium hydroxide and was extracted with ether; the solution was dried ($MgSO_4$) and the ether was removed. Fractional distillation of the yellow oil gave 12.1 g (68%) of 1-[2-(6-methylpyridyl)]-pent-4-ene (**3**) as a colorless liquid: bp 104.5–105° (14 mm); $n^{20}D$ 1.5008; λ_{max}^{EtOH} 266 and 272 mμ (log ε 3.5 and 3.4); ν_{max} 3098, 2948, 2860, 1640, 1590, 1580, 1460, 995, and 910 cm^{-1}; nmr, AB_2 absorption (τ 2.78, 3.16, J = 7 Hz) (3 H), complex absorptions centered at *ca.* τ 3.7 and 5.0 (3 H), a triplet (τ 7.3, J = 7 Hz) (2 H), a singlet (τ 7.5) (3 H), and four other aliphatic protons (τ 7.6–8.6).

Anal. Calcd for $C_{11}H_{15}N$: C, 82.1; H, 9.3; N, 8.7. Found: C, 82.0; H, 9.4; N, 8.9.

Bromination of the Olefin 3.—This reaction was performed several times in different solvents. The procedure used in each case was the same and only one experiment shall be reported.

Bromine (2.4 g) dissolved in dioxane (10 ml) was added dropwise to a stirred solution of olefin **3** (2.4 g) in dioxane (10 ml). When the reaction was complete, the solvent was evaporated under reduced pressure. The residual yellow paste was partitioned between water and chloroform to give an effective separation of the two products **6** and **4**. The relative yields of the two products could be estimated at this state from the ultraviolet absorptions of the two solutions. Solvents used (ratios of cyclized/uncyclized product) follow: carbon tetrachloride (0.19), dioxane (0.96), 2% aqueous dioxane (5.25). Evaporation of the combined chloroform extracts gave a yellow oil which was distilled to give 6-(4,5-dibromopentyl)-2-picoline (**4**) as a colorless liquid: bp 95–96° (0.01 mm); $n^{20}D$ 1.4640; λ_{max}^{EtOH} 266 and 272 mμ (log ε 3.5 and 3.4); ν_{max} 3024, 2858, 1587, 1570, 1451, and 793 cm^{-1}; nmr, AB_2 absorption (τ 2.78 and 3.16, J = 7 Hz) (3 H), a triplet (τ 7.3 J = 7 Hz) (2 H), a singlet (τ 7.5) (3 H), a complex absorption (τ 5.5–6.5) (3 H), and a complex absorption at τ 7.6–8.5 (4 H); mass spectrum, base peak at m/e 106 and parent peaks at m/e 319, 321, and 323 (intensity ratios 1:2:1).

Anal. Calcd for $C_{11}H_{15}NBr_2$: C, 41.2; H, 4.7; N, 4.4; Br, 49.8. Found: C, 41.5; H, 5.1; N, 4.4; Br, 49.6.

(18) E. J. Witzemann, W. Lloyd-Evans, H. Hoss, and E. F. Schroeder, *Org. Syn.*, **11**, 26 (1931).

(19) H. Saikashi, Y. Taniguchi, and H. Ogawa, *Yakugaku Zasshi*, **82**, 1262 (1962); *Chem. Abstr.*, **58**, 1388c (1963).

(20) Melting points and boiling points are uncorrected. Microanalyses were performed by the Microanalytical Section, C. S. I. R. O., Melbourne, Australia, under the direction of Dr. K. W. Zimmerman and Mr. H. J. Jerie. Ultraviolet spectra were recorded in the solvent stated on a Shimadzu photoelectric spectrophotometer Model QR-50. All infrared spectra of solids were measured in potassium chloride disks and those of liquids were measured as liquid films between sodium chloride plates using a Perkin-Elmer Infracord spectrophotometer. Nmr spectra were obtained on a Varian Associates HR 60 spectrometer and were calibrated by the side-band technique. All measurements were made on AnalaR carbon tetrachloride solutions using tetramethylsilane as an internal reference, or on deuterium oxide solutions with acetone or sodium 3-(trimethylsilyl)-1-propane sulfonate as internal references. Mass spectra were measured on an Associated Electronic Industries MS9 spectrometer. When the term nitrogen is used, it should be taken to mean oxygen-free, dry nitrogen, and ether to mean anhydrous, peroxide-free ether.

(21) R. B. Woodward and E. C. Kornfeld, *Org. Syn.*, **29**, 44 (1949).

(22) L. Osuch and R. Levine, *J. Amer. Chem. Soc.*, **78**, 1723 (1956).

Concentration of the aqueous phase yielded **6** which, when crystallized from acetone and acetonitrile, gave white crystals: mp 243–244°; $\lambda_{max}^{H_2O}$ 275 mμ (log ε 3.8); ν_{max} 1620, 1610, 1490, 915, 855, 834, and 810 cm^{-1}; nmr, AB_2 absorption (τ 1.81 and 2.24, J = 7 Hz) (3 H), a broad triplet (τ 6.67, J = 7 Hz) (2 H), a singlet (τ 7.13) (3 H), and a complex absorption (τ 7.18–8.20) (4 H).

Anal. Calcd for $C_{11}H_{15}NB_2$: C, 41.2; H, 4.7; N, 4.4; Br, 49.8. Found: C, 41.1; H, 5.0; N, 4.2; Br, 50.0.

Attempted Cyclization of 6-(4,5-Dibromopentyl)-2-picoline (4).—Several attempts were made to cause dibromide **4** to cyclize. All reactions were studied by ultraviolet spectroscopy and thin layer chromatography (tlc). The following summarizes solvent, concentration (% v/v), temperature, and reaction time (hr): EtOH, 10, 40, 24; EtOH, 10, 78, 24; $HCON(Me_3)_2$, 10, 153, 12; $HOCH_2CH_2OH$, 10, 197, 12; nil, 100, 300, 24. In no case could evidence be found for the cyclized salt **6**.

Reaction between 7 and Sodium Cyanide.—To a solution of **6** (0.32 g) in water (5 ml) was added a solution of sodium cyanide (0.1 g) in water (0.5 ml). The solution was heated to 80° for 1 hr, cooled, and evaporated to 2 ml under reduced pressure. The tarry solid was removed and sodium perchlorate (0.4 g) in water (1 ml) was added. The crystals (46 mg, 15%) which separated were crystallized with difficulty from an acetone–ethanol–water mixture to give almost white crystals of 6-methyl-4-methylene-1,2,3,4-tetrahydroquinolizinium (**5**) perchlorate which decomposed explosively at *ca.* 220° without melting: $\lambda_{max}^{H_2O}$, 277 mμ (log ε 3.85); ν_{max} 3040, 2940, 1655, 1620, 1565, 1480, 1095, and 794 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}NClO_4$: Cl, 13.7. Found: Cl, 14.0.

The chloroplatinate as precipitated with sodium chloroplatinate. The flesh-colored crystals were recrystallized several times from water; the melting point (172–173°) was undepressed by admixture with sample prepared in a similar manner (81% yield) using sodium carbonate instead of sodium cyanide.

Anal. Calcd for $C_{22}H_{28}N_2PtCl_6$: C, 36.4; H, 3.9; Pt, 26.8. Found: C, 35.8; H, 4.0; Pt, 27.0.

Prins Reaction on 1-Chlorobut-3-ene.—As difficulty was experienced in trying to reproduce the yield reported in the literature[23] for the Prins reaction on allyl chloride, a modification of that procedure was followed.

Paraformaldehyde (160 g) was mixed with ether (200 ml) and the mixture was cooled in an ice bath. Fuming sulfuric acid (160 ml) was slowly added over a period of *at least* 4 hr. To the white slurry was added the olefin **2** (40 g) in ether (200 ml) over a period of 1 hr, and the mixture was then allowed to warm to room temperature. The reaction mixture was poured onto a vigorously stirred mixture of ice (750 g) and potassium carbonate (500 g) and stirred thoroughly for 30 min. The mixture was filtered and the residue was washed with ether. The aqueous phase was extracted with ether and the ether extracts were combined and dried ($MgSO_4$). The solvent was removed (12 mm) and the residue was distilled rapidly (0.1 mm) into a cooled receiver. The yellow distillate was shaken with anhydrous potassium carbonate, filtered, and fractionally distilled to yield 49 g (71%) of 4-(2-chloroethyl)-,13-dioxane (**10**): bp 43–44° (0.5 mm); n^{20}D 1.4444; ν_{max} 1305, 1282, 1250, 1151, 1040, 847, and 829 cm^{-1}.

Anal. Calcd for $C_6H_{11}ClO_2$: C, 47.9; H, 7.4; Cl, 23.6. Found: C, 48.0; H, 7.5; Cl, 23.4.

Preparation of 6-{3-[4-(1,3-Dioxanyl)propyl]}-2-picoline (12).—The procedure was similar to the reaction between 2,6-lutidyllithium and 1-chlorobut-3-ene and the product was a colorless oil (64% yield): bp 111–112° (0.5 mm); n^{20}D 1.5173; λ_{max}^{EtOH} 266 and 272 mμ (log ε 3.5 and 3.4); ν_{max} 2940, 2860, 1590, 1580, 1452, 1152, 1120, 1039, and 792 cm^{-1}; nmr, AB_2 absorption (τ 2.78 and 3.18, J = 7 Hz) (3 H), AB quartet (τ 5.05 and 5.37, J = 6 Hz) (2 H), a complex absorption from τ 5.9 to 6.8 (3 H), a triplet at τ 7.25 (J = 7 Hz) (2 H), a singlet at τ 7.5 (3 H), and a complex absorption from τ 7.9 to 8.8 (6 H).

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.6; H, 8.7; N, 6.3. Found: C, 70.5; H, 8.6; N, 6.2.

Cleavage of the 1,3-Dioxane 12.—Lithium iodide (2.5 g) was dissolved in acetic anhydride and boron trifluoride etherate (3.5 ml) was added. To this solution was added the 1,3-dioxane (0.4 g) and the mixture was stirred for 15 min. The mixture was poured onto a slurry of ice (100 g) and potassium carbonate (60 g) and the product was continuously ether extracted. The ether extracts were evaporated and the residue was dried by azeotropic distillation with benzene. The brown viscous oil was chromatographed over B. D. H. silica gel with chloroform. The eluate was collected in 20-ml fractions and fractions 8–60 and 75–125 were combined to yield **11** and **14**, respectively. The solvent was continuously changed to 5% methanol to elute the glycol **13** in fractions 170–210.

The combined fractions (8–60) were evaporated free of chloroform and separated from the small amount of colorless impurity by molecular distillation (10^{-4} mm) giving 80 mg (15%) of colorless viscous oil, 6-(4,6-diacetoxyhexyl)-2-picoline (**11**): n^{20}D 1.4620; λ_{max}^{EtOH} 266 and 272 mμ (log ε 3.5 and 3.4); ν_{max} 2968, 2939, 1738, 1460, 1273, and 1250 cm^{-1}; nmr, AB_2 absorption (τ *ca.* 2.6 and 3.15, J = *ca.* 7.5 Hz) (3 H), a triplet (τ 7.32, J = 7 Hz) (2 H), a singlet (τ 7.56) (3 H), two singlets (τ 8.03 and 8.05) (6 H), a triplet (τ 5.93, J = 7 Hz) (2 H), a quintet (τ 5.00, J = 6 Hz) (1 H), and a complex absorption (6 H) between τ 7.5 and 8.5.

Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.5; H, 7.9; N, 4.8. Found: C, 65.6; H, 7.8; N, 4.8.

By the same procedure fractions 75–125 yielded 180 mg (40%) of 6-(6-acetoxy-4-hydroxyhexyl)-2-picoline (**14**): n^{20}D 1.4310; λ_{max}^{EtOH} 266 and 277 mμ (log ε 3.5 and 3.4); ν_{max} 3430, 2966, 2937, 1730, 1460, 1270, and 1242 cm^{-1}; nmr contained a triplet (τ 5.93) (2 H) and a quintet (τ 6.43) (1 H).

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.9; H, 8.4; N, 5.6. Found: C, 66.7; H, 8.2; N, 5.3.

Fractions 170–210 were combined and evaporated free from solvent. The resultant viscous yellow oil was rechromatographed over B. D. H. alumina with 10% methanol in chloroform. From the eluate was recovered 20 mg (5%) of almost colorless 2-(4,6-dihydroxyhexyl)-6-methylpyridine (**13**): n^{20}D 1.3788; λ_{max}^{EtOH} 266 and 272 mμ (log ε 3.5 and 3.4); ν_{max} 3340, 2925, 1593, 1582, 1540, 1100, 1063, and 830 cm^{-1}; nmr, AB_2 pattern (τ 2.6 and 3.15, J = 7 Hz) (3 H), a broad singlet (τ 5.5) (2 H), a quintet (τ 6.12, J = 6 Hz) overlapping a triplet (τ 6.31, J = 6 Hz) (3 H), a triplet (τ 7.22, J = 7 Hz) (2 H), a singlet (τ 7.55) (3 H), and a complex absorption centered at τ *ca.* 8.5 (6 H); mass spectrum, *m/e* (% of base peak) 91 (20), 107 (100), 120 (38), 134 (22), 162 (34), 164 (45), 191 (20), and 209 (12).

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.9; H, 9.1; N, 6.7. Found: C, 68.4; H, 8.9; N, 6.3.

Treatment of Hydroxyacetate 14 with Phosphorus Tribromide.—The reaction was carried out in dimethoxyethane with phosphorus tribromide at 85° for 1 hr. The mixture was neutralized with aqueous bicarbonate, the solvent was removed under vacuum and the residue repeatedly triturated with benzene. The product was subjected to repeated preparative scale tlc over Merck alumina using 20% carbon tetrachloride in chloroform, to yield 45 mg (16%) of a pale yellow viscous oil, 6-(6-acetoxy-4-bromohexyl)-2-methylpyridine (**15**): n^{20}D 1.5201; λ_{max}^{EtOH} 266 and 272 mμ (log ε 3.5 and 3.4); ν_{max} 2970, 2942, 2868, 1737, 1593, 1580, 1462, and 1265 cm^{-1}; nmr, AB_2 pattern (τ 2.6 and 3.15, J = 7 Hz) (3 H), a triplet (τ 5.95, J = 7 Hz) (2 H), a poorly resolved quintet (τ 6.45, J = *ca.* 5 Hz) (1 H), a triplet (τ 7.2, J = 7 Hz) (2 H), a singlet (τ 7.56) (3 H), and a complex absorption centered at τ 8.4 (6 H).

Anal. Calcd for $C_{14}H_{20}BrNO_2$: C, 53.5; H, 6.4. Found: C, 53.0; H, 6.3.

Hydrolysis of 6-(6-Acetoxy-4-bromohexyl)-2-methylpyridine.—The bromide **15** was dissolved in 50% aqueous dioxane and was rapidly hydrolyzed on adding silver perchlorate. After filtration and thorough extraction with benzene, the product was isolated by preparative scale tlc and was identical with the hydroxyacetate **15**.

Preparation of 4-[6-(2-Picolyl)]butyraldehyde Acetal (16).—The method of preparation was identical with those described above. The product (63%) was a colorless liquid: bp 80–80.5° (0.01 mm); ν_{max} 3076, 2966, 2900, 1590, 1579, 1453, 1370, 1130, 1063, and 800 cm^{-1}; nmr, AB_2 pattern (τ 2.6 and 3.15, J = 7 Hz) (3 H), a triplet (τ 5.58, J = 5 Hz) (1 H), a complex symmetrial absorption centered around τ 6.58 (4 H), a triplet (τ 7.30, J = 7 Hz) (2 H), a singlet (τ 7.57) (3 H), a complex absorption around τ 8.4 (4 H), and a triplet (τ 8.84, J = 7 Hz) (6 H).

Hydrolysis of the Acetal 16.—Generally the hydrolysis was performed on the crude acetal from the above reaction. Fractional distillation of the product gave a colorless liquid (80%): bp 95–96° (1.5 mm); n^{20}D 1.5117; λ_{max}^{EtOH} 266 and 272 mμ (log ε 3.5 and 3.4); ν_{max} 3030, 2840, 2770, 1720, 1588, 1576, 1450, 1150,

(23) C. Price and I. Krishnamurti, *J. Amer. Chem. Soc.*, **72**, 5335 (1950).

1043, 992, and 310 cm^{-1}. The chloroplatinate crystallized from water, mp 184–185° dec.

Anal. Calcd for $C_{20}H_{26}Cl_6N_2O_2Pt$: C, 32.8; H, 3.6; Pt, 26.6. Found: C, 32.2; H, 4.0; Pt, 26.7.

Preparation of 6-(5-Carbethoxypent-4-enyl)-2-picoline (19).—The aldehyde **17** and phosphorane, in equimolar amounts, were heated in refluxing ethanol for 6 hr. After removal of the solvent, and drying of the residue by azeotropic distillation with benzene, petroleum ether (40–60°) was added to the viscous residue causing triphenylphosphine oxide to precipitate. After removal of the precipitate and the solvent, a honey-colored oil (84%) remained. Chromatography over B. D. H. silica gel with chloroform gave a pale yellow oil (62%) which was sufficiently pure for most purposes. An analytical sample was obtained by molecular distillation (10^{-4} mm): n^{20}D 1.5211; λ_{max}^{EtOH} 210, 266, and 272 mμ (log ε 4.1, 3.5, and 3.4).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.1; H, 8.2; N, 6.0. Found: C, 72.2; H, 8.0; N, 6.2.

Bromination of the α,β-Unsaturated Ester 19.—The ester **19** (0.34 g) was dissolved in water (5 ml) by adding dioxane (*ca.* 10 ml). To the vigorously stirred solution was added bromine (0.25 g) in dioxane (5 ml) over a period of 5 min. After stirring for 0.5 hr, the solvent and excess bromine were removed under vacuum. The impure crystals were triturated with chloroform and filtered to yield a buff-colored product (0.46 g, 88%), mp 128–130°. Recrystallization from acetonitrile and from acetone gave an analytical sample of 6-methyl-4-carbethoxybromomethyl-1,2,3,4-tetrahydroquinolizinium bromide (**20**) as white crystals: mp 132–132.5°; $\lambda_{max}^{H_2O}$ 275 mμ (log ε 3.8); ν_{max} 2960, 2906, 2840, 1615, 1582, 1489, 1302, 1257, 1212, 1030, and 802 cm^{-1}.

Anal. Calcd for $C_{14}H_{19}Br_2NO_2$: C, 42.7; H, 4.9; N, 3.6; Br, 40.6. Found: C, 42.9; H, 5.1; N, 3.8; Br, 40.8.

The perchlorate precipitated from aqueous solution and could be crystallized from water. It decomposed explosively at *ca.* 180° without melting: $\lambda_{max}^{H_2O}$ 275 mμ (log ε 3.8); ν_{max} 2962, 2907, 2842, 1616, 1583, 1490, 1306, 1090, 1030, and 800 cm^{-1}.

Anal. Calcd for $C_{14}H_{19}BrClNO_6$: N, 3.4. Found: N, 3.4.

The chloroform extracts were chromatographed over B. D. H silica gel and purified by molecular distillation (10^{-4} mm) to give a pale pink oil. A mass spectral determination gave the following data: *m/e* (% of base peak) 395 (1), 393 (2), 391 (1), 315 (5), 311 (5), 268 (3), 233 (16), 120 (10), and 107 (100).

Treatment of 20 with Base.—Several combinations of base and solvent were studied, but the results were always the same.

The salt **20** (100 mg) was dissolved in water (1.5 ml) and to this was added dropwise a solution of potassium carbonate (50 mg) in water (2 ml). At the end of the addition an oil separated. The product was extracted with carbon tetrachloride, the solvent was removed, and the product was dried by azeotropic distillation with benzene. The product was obtaned as a pale yellow oil (50 mg, 63%) after chromatography over B. D. H. silica gel with carbon tetrachloride: nmr, olefinic and aromatic protons (τ 2.5–3.5) (4 H), a quartet (τ 5.86, J = 7 Hz) (2 H), a triplet (τ 7.3, J = 7 Hz) (2 H), a singlet (τ 7.5) (3 H), a complex multiplet (τ 7.5–8.4) (4 H), and a triplet (τ 8.7, J = 7 Hz); mass spectrum, *m/e* (% of base peak), 107 (100), 108 (32), 120 (18), 158 (10), 230 (32), 231 (9), 311 (12), and 313 (12).

Anal. Calcd for $C_{14}H_{18}BrNO_2$: C, 53.9; H, 5.8; Br, 25.6; N, 4.5. Found: C, 53.7; H, 5.6; Br, 25.2; N, 4.5.

Registry No.—**3,** 15981-94-9; **4,** 15981-95-0; **5** perchlorate, 15982-08-8; **5** chloroplatinate, 12244-22-3; **6** bromide, 15981-96-1; **10,** 15981-97-2; **11,** 15981-98-3; **12,** 15982-00-0; **13,** 15982-01-1; **14,** 15982-02-2; **15,** 15981-99-4; **16,** 15982-03-3; **17** chloroplatinate, 12244-21-2; **19,** 15982-04-4; **20** bromide, 15982-05-5; **20** perchlorate, 15982-06-6; **21,** 15982-07-7.

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Reaction of Aziridine and Oxirane Derivatives with Diphenyliodonium Iodide[1,2]

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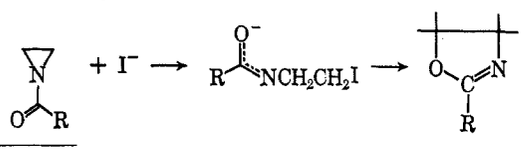
The reaction of diphenyliodonium iodide with suitably substituted 2-benzoylaziridines affords 2,5-diaryloxazoles and the corresponding α,β-unsaturated ketone. The removal of the nitrogen atom and the subsequent formation of the corresponding olefin is found to be a general phenomenon. The mechanism proposed for the deamination involves coordination of diphenyliodonium iodide with the unshared electrons of the carbonyl oxygen followed by proton loss and subsequent elimination. The formation of the substituted 2,5-diaryloxazole proceeds by carbon–carbon cleavage of the aziridine ring to produce an intermediate tight ion pair. The reaction between diphenyliodonium iodide and α,β-epoxy ketones causes a major fragmentation of the oxide ring and affords a mixture of aryl acids and ketones.

1-Aroylaziridines are known to be readily isomerized into 2-aryl-Δ^2-oxazolines by the action of aluminum halides, heat, or nucleophilic reagents.[4–11] These rearrangements are formally analogous to the vinylcyclopropane–cyclopentene isomerization and the details of the transformation have been elegantly elucidated by Heine and coworkers.[11] The isomerization by nucleophilic reagents has been explained by a reaction scheme involving attack by a nucleophile, such as iodide ion, on one of the carbon atoms of the aziridine ring to form a 2-iodoethylamine anion (eq 1). In a subsequent step the ion cyclizes to the oxazoline and regenerates the iodide ion. Substituted 1-acyl-2-alkylaziridines also undergo pyrolytic isomerization to form N-allylamides.[12,13] Kinetic and stereochemical



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