A Facile Synthesis of Azetidines

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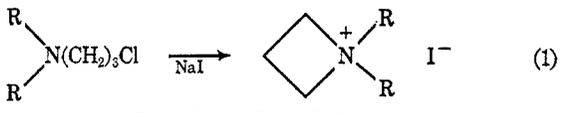
A new method for the preparation of azetidines, particularly the parent compound and its lower homologs, is described. Tertiary azetidines were formed by cyclization of the appropriate N-substituted N-(2-carbethoxyethyl)-3-aminopropyl chlorides in the presence of sodium carbonate. Secondary azetidines, including the parent compound, could be obtained by saponification and subsequent cleavage of 1-(2-carbethoxyethyl)azetidines. The saponification with dry potassium hydroxide proceeded exothermically to form the corresponding potassium 3-azetidinopropionates which could be freed of ethanol under vacuum. Facile cleavage of the potassium salts at 250° in the presence of potassium hydroxide furnished nearly quantitative yields of the secondary azetidines.

Although considerable interest in the chemistry of small-ring heterocycles has been generated in recent years by cancer research programs, the preparation and chemistry of azetidines, especially those without C substituents, or those with a single substituent on carbon, have been relatively unexplored. The methods of preparation of azetidine and its lower homologs are, in general, characterized by poor yields and/or cumbersome preparative procedures.[1]

In this paper we describe a method whereby a variety of azetidines, both secondary and tertiary, can be prepared quickly without employing high-dilution techniques. Simple distillations of the final products are sufficient for purification, and, in general, intermediates need not be purified. Operations lend themselves to moderate scale-up [1-(2-carbethoxyethyl)azetidine (**5a**) has been prepared in 200-g batches]. The method shows promise of being generally applicable with a possible exception of 2-substituted azetidine preparations; here secondary halides are generated which are relatively inert toward ring closure (see the Experimental Section for details).

Discussion

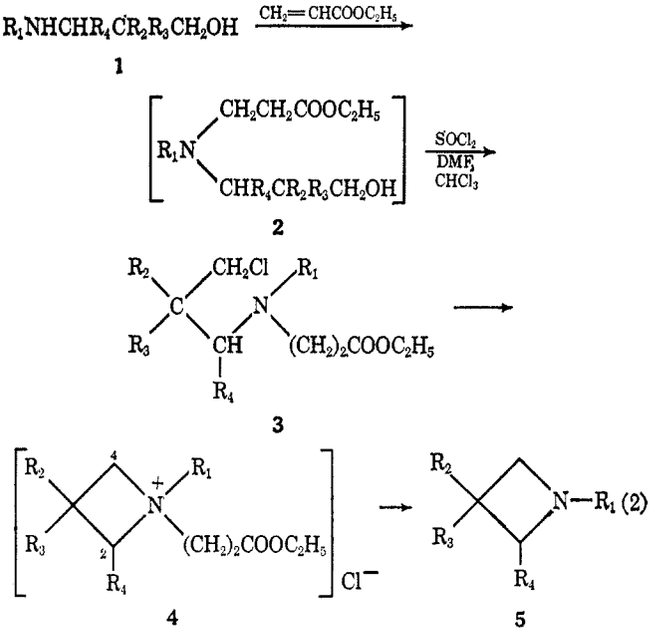
In contrast with high-dilution techniques which are usually required to form azetidine rings, several N,N-dialkyl-β-aminopropyl halides are reported to undergo spontaneous cyclization to the corresponding azetidinium halides (eq 1).[2,3] Based on this observation, and



(1)

R = C_2H_5, C_3H_7, C_4H_9

on our experience with the facile decomposition of 1-(2-carbethoxyethyl)-1-methyl-3,3-di-*n*-pentylazetidinium iodide to the tertiary azetidine,[4] it appeared to be feasible to cyclize N-substituted (2-carbethoxyethyl)-3-aminopropyl halides to the corresponding azetidinium quaternary salts, and subsequently to form tertiary azetidines by a Hofmann-type decomposition (eq 2). Many attempts to prepare various 1-(2-carbethoxyethyl)azetidinium salts (chlorides, iodides, fluoroborates) resulted in gummy products which defied purification. By refluxing **3a** in aqueous solution, however, 1-(2-carbethoxyethyl)azetidine (**5a**) was obtained, but the yield was poor and the product was contaminated.



a, $R_1 = (CH_2)_2COOC_2H_5$; $R_2 = R_3 = R_4 = H$
b, $R_1 = (CH_2)_2COOC_2H_5$; $R_2 = C_2H_5$; $R_3 = R_4 = H$
c, $R_1 = (CH_2)_2COOC_2H_5$; $R_2 = R_3 = n\text{-}C_5H_{11}$; $R_4 = H$
d, $R_1 = CH_2C_6H_5$; $R_2 = R_3 = R_4 = H$
e, $R_1 = CH_2C_6H_5$; $R_2 = R_3 = H$; $R_4 = CH_3$

With a technique similar to that previously described,[4] pure **5a** was obtained from **3a** in a gas chromatograph injection port which had been packed with potassium hydroxide on Celite 545.

A variety of other cyclization procedures with various types of apparatus, including rotating flasks, hot tubes, etc., was carried out. The most successful (70% yield) and reproducible operation involved heating an intimate mixture of anhydrous sodium carbonate and the appropriate chloride with removal of the cyclized material by distillation as soon as it was formed. If **5a** was not removed from the reaction site soon after formation, no cyclized product was obtained, and only a nonvolatile oil could be extracted from the reaction mixture. The infrared spectrum of this oil was nearly identical with that of **5a**, suggesting a secondary reaction of **5a** and either **3a** or the cyclic azetidinium ion intermediate (**4a**), to form molecules of comparatively high molecular weight. The tendency of azetidines **5** to polymerize under the influence of mild alkylating agents was demonstrated with **5a** and **5d** and *n*-butyl *p*-toluenesulfonate. (See the Experimental Section.)

(1) James A. Moore, "The Chemistry of Heterocyclic Compounds," Vol. 10, Part II, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, Chapter VII.
(2) C. F. Gibbs and C. S. Marvel, *J. Am. Chem. Soc.*, **56**, 725 (1934).
(3) C. A. Grob and F. L. Jenney, *Tetrahedron Letters*, **23**, 25 (1960).
(4) D. H. Wadsworth and O. E. Schupp, III, *J. Heterocyclic Chem.*, **3**, 230 (1966).

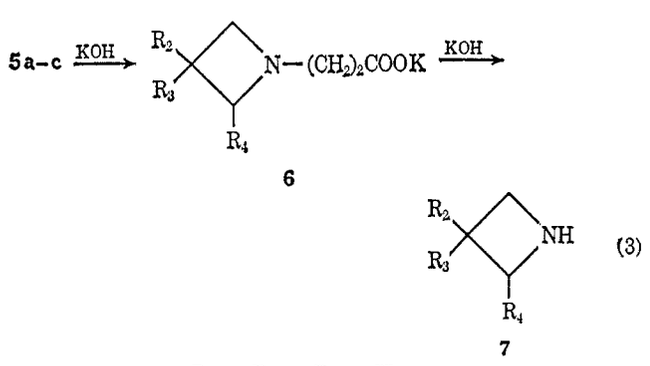
No organic bases have yet been found effective in cyclizing **3** to **5** because of the high-temperature stability and nonvolatility required of such a base.

Usually, azetidines were formed in 50–75% yields, with little, if any, volatile by-product. 1-Benzyl-2-methylazetidine (**5e**), however, was obtained in only 19% yield, the remainder of the starting material having been converted to ethyl N-benzyl-N-(3-chlorobutyl)-3-aminopropionate, $C_6H_5CH_2N(CH_2CH_2COOC_2H_5)CH_2CH_2CHClCH_3$ (**8**). The appearance of this isomeric chloride provided strong evidence for the existence of the discrete intermediate azetidinium ion (**4e**). Thus, the equilibrium **3e** $\rightleftarrows$ **4e** was disturbed by rupture of the 1,2 bond to form **8**,[5] a much less reactive chloride which showed little tendency toward cyclization and accumulated in the reaction medium.

A number of 3-aminopropyl chlorides, prepared according to eq 2, were used to determine the generality of the reaction. All 3-(*sec*-amino)propanols were prepared by standard procedures[6] (see the Experimental Section for details).

Yields in all steps were generally good; although in many cases the preparation of analytically pure material was impractical, crude products could be used directly in the subsequent steps. Proposed structures were all substantiated by infrared analysis. All ethyl acrylate adducts had infrared absorptions at 5.8 μ, characteristic of saturated esters. Secondary amines and amino alcohols exhibited characteristic absorptions at 3.0–3.1 μ. The reaction of sodium cyanide with α-bromo esters presented some unforeseen problems. With alcohol–water as the solvent only a trace amount of the desired product was formed. In utilizing dimethylformamide as the solvent, great care had to be exercised, both in avoiding an excess of bromide during the addition to the sodium cyanide solution and in product isolation to prevent formation of high-boiling by-products.[7]

Secondary azetidines were prepared by heating their N-(2-carbethoxyethyl) precursors with 2 equiv of potassium hydroxide at 250° and distilling out the amine. The parent compound (**7a**) was prepared in this manner in nearly quantitative yield, requiring only a simple redistillation for purification. 3-Ethylazetidine (**7b**) and 3,3-di-*n*-pentylazetidine (**7c**) were also prepared by this procedure (eq 3).



(3)

a, $R_2 = R_3 = R_4 = H$
b, $R_2 = C_2H_5$; $R_3 = R_4 = H$
c, $R_2 = R_3 = n\text{-}C_5H_{11}$; $R_4 = H$

The intermediate salt, potassium 3-azetidinopropionate (**6a**), was also isolated. An attempted cleavage of this salt without additional potassium hydroxide produced no azetidine, even at a temperature of 270°. With an equivalent amount of potassium hydroxide, however, azetidine was formed in 81% yield.

Our method has proved to be convenient for preparation of both secondary and tertiary azetidines, ranging from the parent compound to azetidines having quite bulky ring substituents. Yields are, in general, quite good, and laboratory procedures and purifications are comparatively simple.

Experimental Section

Preparation of Azetidine (7a). A. Diethyl N-(3-Hydroxypropyl)-3,3′-iminopropionate (2a).—Eastman Technical Grade 3-amino-1-propanol (50.0 g, 0.67 mole) was added carefully to 250 ml of ethyl acrylate (stabilized with 0.10 g of dinitrobenzene) and refluxed overnight. The excess ethyl acrylate was stripped off *in vacuo*, furnishing 182 g of product **2a** (99% yield). Attempts to distill the material resulted in decomposition; however, the crude product was of sufficiently high purity to be used for subsequent conversion to the corresponding chloride.

B. Diethyl N-(3-Chloropropyl)-3,3′-iminopropionate (3a). General Procedure for 3-Aminopropyl Chloride Preparations.—A solution of 100 g (0.0364 mole) of **2a** in 400 ml of chloroform containing 10 ml of dimethylformamide was treated dropwise with 47.5 g (0.40 mole) of thionyl chloride dissolved in 50 ml of chloroform. The temperature was maintained at 20–30° by cooling. After completion of the addition, the reaction mixture was stirred at room temperature for 0.5 hr and poured into excess, aqueous sodium bicarbonate. The chloroform layer was separated, washed with water, dried over sodium sulfate, and evaporated *in vacuo*, with a minimum of heat. Distillation of the product **3a** resulted in considerable decomposition with a corresponding loss of yield. Crude **3a** was of good vapor phase chromatographic purity, however, and needed only to be separated from a small amount of residual poly(ethyl acrylate), formed during the preparation of **2a**. This was easily accomplished by pouring the crude **3a** into excess petroleum ether (bp 35–60°) and separating the insoluble gum. A yield of 106 g (99%) with a vpc purity of 95% was obtained.

C. 1-(2-Carbethoxyethyl)azetidine (5a). General Procedure for Cyclization of 3-Aminopropyl Chlorides.—A mixture of 75.0 g (0.256 mole) of **3a**, 150 g of sodium carbonate powder, and 800 g of copper shot (to facilitate heat transfer) was heated at 165–205° (20 mm) in a round-bottomed flask fitted with a vacuum distillation head. The resulting distillate was redistilled to separate ethyl acrylate and any entrained **3a** to furnish 28.1 g (70% yield) of **5a**, bp 56° (0.40 mm).

Anal. Calcd for $C_8H_{15}NO_2$: C, 61.0; H, 9.6; N, 8.9. Found: C, 61.3; H, 9.6; N, 8.8.

Azetidine **5a** could also be prepared in an aqueous reaction medium according to the following precedure. A 20% mixture of amino chloride **3a** in water was refluxed for 2 hr, with rapid stirring. The homogeneous solution (vpc showed complete disappearance of starting material) was evaporated to dryness *in vacuo*, and the gummy residue was shaken with excess, moist sodium carbonate and chloroform (care must be taken to avoid any prolonged contact between free **5a** and aqueous base, since the ester is rapidly hydrolyzed). After drying over sodium sulfate, the chloroform was evaporated and the residue was distilled to furnish a 22% yield of **5a** of 98% vpc purity. This low yield may reflect the extreme ease of hydrolysis of **5a**, which could be accomplished in water, even without added base.

D. Azetidine (7a). General Procedure for Cleavage of 1-(2-Carbethoxyethyl)azetidines.—A mixture of 49.6 g (0.31 mole) of 1-(2-carbethoxyethyl)azetidine (**5a**) and 39.0 g (0.70 mole) of powdered potassium hydroxide was mixed cautiously, the temperature being maintained below 80° by cooling. After completion of the spontaneous reaction, the pasty mixture was heated slowly to 200° under water-pump vacuum to remove all traces of ethanol. The vacuum was removed and heating was

(5) C. Fodor, *J. Am. Chem. Soc.*, **88**, 1040 (1966).

(6) The preparation of bis-2-carbethoxyethylamines was accomplished without isolating the intermediate monoadducts.

(7) In a similar preparation of ethyl α-cyanopropionate, the high-boiling material was separated by preparative gas chromatography into two products which were assigned the diastereoisomeric structures of $C_2H_5OCOC^*H(CH_3)C^*(CH_3)(CN)COOC_2H_5$ on the basis of their infrared and mass spectra.

continued to 270° until azetidine distillation was complete. The product (**7a**) obtained in 98% yield (17.4 g, bp 62°) showed a vpc purity of 99% on a Carbowax column. Reaction with *p*-toluenesulfonyl chloride gave 1-(*p*-toluenesulfonamido)azetidine with physical properties and infrared spectrum identical with an authentic sample prepared according to Vaughn, *et al.* [lit.[8,9] bp 62°, mp (*p*-toluenesulfonamide) 121°, mp (picrate) 166–167°].

Intermediate potassium salt **6a** was isolated from the pasty reaction mixture of **5a** and potassium hydroxide by washing the paste thoroughly with ethyl ether and drying the white product *in vacuo*.

Anal. Calcd for $C_6H_{10}KNO_2$: C, 43.1; H, 6.0; K, 23.4. Found: C, 43.1; H, 6.2; K, 23.3.

Heating 3.5 g (0.021 mole) of **6a** with 1.3 g (0.023 mole) of potassium hydroxide to 250° furnished 0.95 g of chromatographically pure **7a** (81% yield).

Preparation of 3-Ethylazetidine (7b). A. Ethyl 2-Cyanobutyrate (9).—A stirred suspension of 17.7 g (0.36 mole) of sodium cyanide in 150 ml of dimethylformamide and 15 ml of water was treated dropwise with 47.0 g (0.24 mole) of ethyl 2-bromobutyrate. The temperature during the course of addition was maintained at 25–35°, and the addition rate was adjusted so that no build-up of starting bromo ester occurred. Periodic checks of the starting-material concentration were made by vapor phase chromatography using 10% diisodecylphthalate on 60–80 mesh Diatoport W. If the starting-material concentration became too high, a high-boiling by-product was formed, and product yields dropped drastically (see the Discussion and ref 7). Upon completion of the addition, the reaction mixture was stirred at room temperature until no starting material remained, and was poured into 1.5 l. of ethyl ether. The ether layer was washed with cold, 5% hydrochloric acid and water, and dried over sodium sulfate and sodium bicarbonate. Evaporation of the solvent and distillation of the residue furnished 24.3 g of product **8** (72% yield), bp 58° (0.60 mm), 97% vpc purity (lit.[10] bp 208.4–209.4°).

B. Diethyl N-(2-Hydroxymethylbutyl)-3,3′-iminodipropionate (2b).—Ethyl 2-cyanobutyrate (**9**, 29.7 g, 0.21 mole) was reduced with 16.0 g (0.42 mole) of lithium aluminum hydride by refluxing in 100 ml of tetrahydrofuran for 4 hr. The reaction mixture was decomposed with saturated aqueous ammonium chloride, filtered, treated with 50 ml of ethyl acrylate (containing a polymerization inhibitor)[11] on a steam bath for 1 hr, and stripped on a rotary evaporator. The inorganic residue from the lithium aluminum hydride reduction was found to contain substantial amounts of amino alcohol which could not be removed by further washing. Consequently, the residue was boiled for 30 min with excess ethyl acrylate and filtered, and the ethyl acrylate filtrate was combined with the main reaction mixture and refluxed overnight. After the volatile material had been stripped *in vacuo*, the residue was taken up in petroleum ether to separate any poly(ethyl acrylate). Evaporation of the petroleum ether furnished 50 g (50% yield) of amino alcohol **2b**, which was of sufficient purity for subsequent treatment with thionyl chloride.

C. Diethyl N-(2-Chloromethylbutyl)-3,3′-iminodipropionate (3b).—Treatment of **2b** by the general procedure furnished **3b** in 87% yield. Although decomposition occurred with attempted distillation, the crude material was of sufficient purity for subsequent cyclization.

D. 1-(2-Carbethoxyethyl)-3-ethylazetidine (5b).—Cyclization of **3b** furnished a 62% yield of **5b**, bp 59–60° (0.50 mm).

Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.8; H, 10.3; N, 7.6. Found: C, 65.1; H, 10.6; N, 7.5.

E. 3-Ethylazetidine (7b).—Cleavage of **5b** furnished an 87% yield of **7b**: bp 106–108°, mp (picrate) 128–129°.

Anal. Calcd for $C_{11}H_{14}N_4O_7$: C, 41.9; H, 4.5; N, 17.8. Found: C, 41.8; H, 4.4; N, 17.9.

Preparation of 3,3-Di-*n*-pentylazetidine (5c). A. Ethyl 2-Cyano-2-*n*-pentylheptanoate (10).—A mixture of 368.0 g (2.4 moles) of 1-bromopentane and 126.0 g (1.1 moles) of ethyl cyanoacetate dissolved in 205 ml of absolute ethanol was treated with sodium ethoxide solution (prepared from 53.6 g of sodium and 825 ml of absolute ethanol). The addition was carried out at reflux over a 1-hr period, and the resulting solution was refluxed for an additional 3.5 hr. The reaction mixture was evaporated in an air stream overnight, washed with water, sodium thiosulfate solution, and water, and distilled to furnish 252.0 g (89.5% yield) of product **10**, bp 98° (0.15 mm).

Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.2; H, 10.7. Found: C, 70.9; H, 10.5.

B. 2-Aminomethyl-2-*n*-pentylheptanol (1c).—Ethyl 2-cyano-2-*n*-pentylheptanoate (**10**, 20.0 g, 0.79 mole) was reduced with 15.0 g (0.39 mole) of lithium aluminum hydride by refluxing for 6 hr in ether. The reaction mixture was decomposed with excess aqueous ammonium chloride and filtered, and the resulting ether solution was dried over sodium sulfate. Evaporation of the solvent furnished 13.5 g of product **1c** (97.5% yield). Infrared analysis showed no residual CN or $COOC_2H_5$, and the product was used directly without further purification.

C. Diethyl N-(2-Hydroxymethyl-2-*n*-pentylheptyl)-3,3′-iminodipropionate (2c).—Crude amino alcohol **1c** (13.5 g, 0.063 mole) was refluxed overnight with 75 ml of ethyl acrylate containing a small amount of polymerization inhibitor.[11] The excess ethyl acrylate was evaporated and the resulting product was taken up in petroleum ether to separate any poly(ethyl acrylate). Evaporation of the solvent furnished 25.1 g (97% yield) of product **2c** which could be used without further purification.

Anal. Calcd for $C_{23}H_{45}NO_5$: C, 66.5; H, 10.9; N, 3.4. Found: C, 66.7; H, 10.8; N, 3.4.

D. Diethyl N-(2-Chloromethyl-2-*n*-pentylheptyl)-3,3′-iminodipropionate (3c).—Treatment of **2c** by the general procedure with thionyl chloride furnished **3c** in 90% yield. Purification by distillation was not attempted, and the product was used crude for cyclization.

E. 1-(2-Carbethoxyethyl)-3,3-di-*n*-pentylazetidine (5c).—Cyclization of **3c** by the general procedure (with the exception of a decomposition pressure maintained at 0.10 mm) furnished **5c** in 48% yield, bp 89–92° (0.003 mm).

Anal. Calcd for $C_{18}H_{35}NO_2$: C, 72.7; H, 11.8; N, 4.7. Found: C, 72.8; H, 11.7; N, 4.6.

F. 3,3-Di-*n*-pentylazetidine (7c)—Cleavage of **5c** at 0.10 mm furnished **7c** in 50% yield, bp 72–78° (0.03 mm).

Anal. Calcd for $C_{13}H_{27}N$: 79.1; H, 13.8; N, 7.1. Found: C, 79.1; H, 13.6; N, 6.9.

Preparation of 1-Benzylazetidine (5d). A. N-Benzyl-3-amino-1-propanol (1d).—An alcoholic solution of 3-benzylideneimino-1-propanol [prepared by mixing 75.0 g (1.0 mole) of 3-amino-1-propanol and 106.0 g (1.0 mole) of benzaldehyde in 200 ml of ethanol] was treated with hydrogen (60 psi) and 0.5 g of Adams catalyst at room temperature for 2 hr. The resulting reaction mixture was stripped of ethanol, furnishing 155 g of **1d** (96% yield) of 97% vpc purity.

B. Ethyl N-Benzyl-N-(3-hydroxypropyl)-3-aminopropionate (2d).—A 50.0-g sample of **1d** was dissolved in 100 ml of ethyl acrylate (containing a small amount of polymerization inhibitor)[11] and refluxed overnight. Excess ethyl acrylate was stripped off *in vacuo*, furnishing 81.0 g (100% yield) of product **2d** which was used without further purification.

C. Ethyl N-Benzyl-N-(3-chloropropyl)-3-aminopropionate (3d).—Treatment of **2d** with thionyl chloride by the standard procedure furnished a 96% yield of **3d** of 95% vpc purity. The crude product was used directly for cyclization.

D. N-Benzylazetidine (5d).—Cyclization of **3d** by the general procedure furnished a 73% yield of 1-benzylazetidine (**5d**), bp 87° (0.10 mm).

Anal. Calcd for $C_{10}H_{13}N$: C, 81.6; H, 8.9; N, 9.5. Found: C, 81.8; H, 8.8; N, 9.5.

Preparation of 1-Benzyl-2-methylazetidine (5e). A. Ethyl N-Benzyl-3-aminobutyrate (11).—A solution of 30.0 g (0.32 mole) of benzylamine in 100 ml of ethyl crotonate was refluxed for 1 hr and stripped *in vacuo*. The oily, dark residue was poured into petroleum ether, the resulting insoluble gum was separated, and the petroleum ether solution was evaporated on the steam bath. The resulting product (**11**, 46.0 g, 74.3% yield) had an infrared spectrum compatible with the desired structure and a 97% vpc purity [lit.[10] bp 172–174° (24 mm)].

B. N-Benzyl-3-amino-1-butanol (1e).—Reduction of 22.1 g (0.10 mole) of **11** with 7.6 g (0.20 mole) of lithium aluminum hydride was accomplished by refluxing in ethyl ether for 2.5 hr. The reaction mixture was decomposed with excess aqueous ammonium chloride, furnishing 17.9 g (100% yield) of product **1e** of 97% vpc purity [lit.[10] bp 173–174° (23 mm)].

(8) W. F. Vaughn, R. S. Klonowski, R. S. McElhinney, and B. B. Millward, *J. Org. Chem.*, **26**, 138 (1961).

(9) S. Gabriel and J. Weiner, *Ber.*, **21**, 2669(1888).

(10) J. C. Hessler, *Am. Chem. J.*, **22**, 169 (1899).

(11) Dinitrobenzene (0.10 wt %) is a suitable polymerization inhibitor.

C. Ethyl N-Benzyl-N-(3-hydroxy-2-butyl)-3-aminopropionate (2e).—A solution of 18.0 g (0.10 mole) of **1e** in 50 ml of ethyl acrylate containing a small amount of polymerization inhibitor was refluxed overnight and stripped *in vacuo*. The residue was taken up in petroleum ether, the insoluble gum was separated and discarded, and the solution was treated with decolorizing carbon. Solvent evaporation furnished 18.6 g of product **2e** (66% yield) of 90% vpc purity. An infrared spectrum was compatible with the desired structure.

D. Ethyl N-Benzyl-N-(3-chloro-2-butyl)-3-aminopropionate (3e).—Treatment of **2e** by the general thionyl chloride procedure furnished a 95% yield of product of 90% vpc purity. The crude material was used directly for subsequent cyclization.

E. 1-Benzyl-2-methylazetidine (5e).—The general cyclization procedure furnished only a 19% yield of product **5e**, bp 106–108° (23 mm).

Anal. Calcd for $C_{11}H_{15}N$: C, 82.0; H, 9.3; N, 8.7. Found: C, 81.9; H, 9.3; N, 8.4.

After the evolution of the desired product ceased, the vacuum was increased to 0.10 mm and the resulting distillate was collected, bp 153° (1.1 mm).

Anal. Calcd for $C_{16}H_{24}ClNO_2$: C, 64.6; H, 8.1; Cl, 11.9; N, 4.7. Found: C, 64.9; H, 8.2; Cl, 12.0; N, 4.7.

This chloride, which proved to be isomeric with starting material **3d**, had an nmr and mass spectrum compatible with the structure of ethyl 3-(N-benzyl-N-3-chlorobutylamino)propionate.

Preparation of 1,1-Di-*n*-pentylazetidinium Iodide (12).—A solution of 7.0 g (0.030 mole) of 3-(N,N-di-*n*-pentyl)aminopropyl chloride and 5.0 g (0.033 mole) of sodium iodide in 50 ml of acetonitrile was refluxed for 16 hr. The solvent was evaporated and the residue was taken up in chloroform and filtered to remove the insoluble, inorganic residue. Evaporation of the chloroform and crystallization of the residue from acetone–ethyl ether furnished 3.1 g of **12**, mp 64–66°.

Anal. Calcd for $C_{13}H_{28}IN$: C, 48.0; H, 8.7; I, 39.0. Found: C, 47.8; H, 8.5; I, 38.8.

Attempted Quaternization of 1-(2-Carbethoxyethyl)azetidine and 1-Benzylazetidine.—Equimolar mixtures of either **5a** or **5b** and *n*-butyl *p*-toluenesulfonate, after standing at room temperature overnight, produced a viscous gum. Vapor phase chromatography of these products showed no **5**; however, nearly all of the *n*-butyl *p*-toluenesulfonate remained unchanged. It was found that as little as 0.1 mole of *n*-butyl *p*-toluenesulfonate per mole of **5a** or **5b** caused a conversion to nonvolatile products with infrared spectra very similar to those of the parent azetidines **5a** or **5b**.

Registry No.—**5a**, 7730-42-9; **7a**, 503-29-7; **6a**, 7730-43-0; **5b**, 7730-44-1; 1-(*p*-toluenesulfonamido)azetidine, 7730-45-2; picrate of **7a**, 7730-46-3; **7b**, 7730-47-4; picrate of **7b**, 7730-36-1; **2c**, 7775-87-3; **5c**, 7042-17-3; **7c**, 7042-16-2; **5d**, 7730-39-4; **5e**, 7730-40-7; **12**, 7730-41-8; **10**, 7730-35-0.

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Steric Effects in P^{31} Nuclear Magnetic Resonance

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Several series of esters of the acids of phosphorus in which a bulky tertiary alkyl ester group was replaced successively with an ethyl (or methyl) group were prepared and analyzed by P^{31} nuclear magnetic resonance. For the esters of quadruply connected phosphorus (trialkyl phosphates, thiophosphates, selenophosphates, and dialkyl phosphonates), replacement of the bulky tertiary alkyl ester group by an ethyl or methyl group gave a nearly linear downfield shift. However, in the case of triply connected phosphorus (the trialkyl phosphites), the first replacement of the bulky tertiary alkyl ester group gave a large upfield increase in chemical shift followed by the usual downfield progression. This is interpreted on the basis of the quantum-mechanical theory of P^{31} chemical shifts in terms of fractional-degree bond-angle changes.

As part of a study[2] of *t*-butyl phosphites carried out several years ago, it was noted that the P^{31} nuclear magnetic resonance (nmr) chemical shift did not vary linearly across the substitution series of compounds $P(OC_2H_5)_{3-i}[OC(CH_3)_3]_i$, for $i = 0$, 1, 2, and 3, as is the case for most mixed-ester systems. As a result, a number of compounds were prepared for an investigation of the effect of bulky alkyl groups on the P^{31} chemical shifts of completely esterified phosphorus-based acids. These data have not been reported until now, pending the elucidation of the theory of P^{31} chemical shifts.[3,4]

Experimental Section

Nmr Spectra.—A Varian HR-60 high-resolution spectrometer using a Model V-4311 fixed-frequency radiofrequency unit operating at 24.288 Mc was used for the P^{31} nmr measurements. Referencing (with positive shifts being upfield) was done by audio side-band modulation, using as external references 85% H_3PO_4 (chemical shift, $\delta = 0.0$ ppm) and triphenyl phosphite, $(C_6H_5O)_3P$ (chemical shift, $\delta = 126.8$ ppm), sealed in 1-mm-o.d. capillary tubes inserted in the sample. Peak positions were reproducible to within ±0.1–0.2 ppm. Unless indicated otherwise, published chemical shifts that were pertinent were redetermined in order to give maximum consistency in the comparisons given here.

Synthesis of Esters.—Tri-*t*-butyl phosphite ($\delta_P = -138.2$ ppm and $\delta_H = 1.34$ ppm, the latter being internally referenced from tetramethylsilane), phosphate ($\delta_P = +13.3$ ppm, $\delta_H = -1.46$ ppm), thiophosphate ($\delta_P = -41.2$ ppm, $\delta_H = -1.53$ ppm), selenophosphate ($\delta_P = -31.1$ ppm, $\delta_H = -1.57$ ppm), and di-*t*-butyl phosphonate ($\delta_P = +3.8$ ppm, $\delta_H = -1.45$ ppm and $J_{H-P} = 678$ cps) were prepared according to the procedures already described.[2] The mixed esters of phosphorous acid were made by analogous procedures from $(RO)_2PCl$ or $(RO)PCl_2$ (where R = CH_3 or C_2H_5) and the branched alcohol in ether as solvent, using triethylamine as the base. The mixed esters of the phosphates, thiophosphates, selenophosphates, and phosphonates were obtained by the oxidation of the corresponding trivalent esters with oxygen, sulfur, or selenium, as were the esters derived from *t*-pentyl or 1,1-dimethylallyl alcohol, acetone cyanohydrin, and neopentyl, *sec*-butyl, or isopropyl alcohol. Of the compounds prepared for this study, the following appear to be new to the literature: $[CH_3(C_2H_5)CHO]_2P(OC_2H_5)$, $\delta_P = -138.4$ ppm; $[CH_3(C_2H_5)CHO]_3P$, $\delta_P = -139.1$; $[(CH_3)_3CCH_2O]P(OC_2H_5)_2$, $\delta_P = -137.2$ ppm; $[(CH_3)_3CCH_2O]_2P(OC_2H_5)$, $\delta_P = -137.2$ ppm; $[(CH_3)_3CO]P(OC_2H_5)_2$, $\delta_P = -134.0$ ppm; $[(CH_3)_3CO]_2P(OC_2H_5)$, $\delta_P = -131.1$ ppm; $[(C_2H_5)(CH_3)_2CO]_3P$, $\delta_P = -138.6$ ppm; $[(CH_2{=}CH)(CH_3)_2CO]P(OC_2H_5)_2$, $\delta_P = -133.9$ ppm; $[(CH_2{=}CH)(CH_3)_2CO]_2P$-

(1) Hooker Research Center, Niagara Falls, N. Y. 14302.

(2) V. Mark and J. R. Van Wazer, *J. Org. Chem.*, **29**, 1006 (1964).

(3) J. H. Letcher and J. R. Van Wazer, *J. Chem. Phys.*, **44**, 815 (1966). Owing to a clerical error, the values of $f(3)$ and $f(4)$ on pp 825, 826, and 829 were incorrectly given and should be 0.018 and 0.0067, respectively.

(4) J. H. Letcher and J. R. Van Wazer, *ibid.*, **44**, 2916 (1966).