Elution with petroleum ether gave 0.1 g (40%) of bi-4,4'-(4-benzyl-2-phenyl-Δ^2-oxazolin-5-one) (**9b**), mp 210 °C, after recrystallization from a mixture (4:1) of petroleum ether and benzene. IR spectrum (KBr): ν_{max} 1839 ($\nu_{C=O}$), 1646 ($\nu_{C=N}$), 1437, 1302, 1276, 957, 862, 676 cm^{-1}.

Anal. Calcd for $C_{32}H_{24}N_2O_4$: C, 76.80; H, 4.80; N, 5.60. Found: C, 77.32; H, 4.49; N, 5.33.

Further elution of the column with a mixture (1:1) of petroleum ether and benzene gave 0.04 g (29%) of benzamide, mp 127–128 °C (mmp).

In a repeat run, a mixture of 0.25 g (1 mmol) of **3b** and 2 g of nickel peroxide in benzene (70 mL) was stirred at room temperature for 16 h. Workup of the mixture as in the earlier case gave 0.15 g (60%) of **9b**, mp 210 °C (mmp).

Irradiation of Bi-4,4'-(4-benzyl-2-phenyl-Δ^2-oxazolin-5-one) (9b). A solution of **9b** (0.50 g, 1 mmol) in benzene (450 mL) was irradiated for 1.5 h under a nitrogen atmosphere. Removal of the solvent under vacuum gave a product mixture which was chromatographed over neutral alumina. Elution with petroleum ether gave 0.2 g (40%) of the unchanged starting material, mp 210 °C (mmp), after recrystallization from a mixture (4:1) of petroleum ether and benzene.

Subsequent elution with a mixture (1:1) of benzene and petroleum ether gave 0.14 g (29%) of benzamide, mp 127–128 °C (mmp).

Sensitized Photooxygenation of 4-Benzylidene-2-phenyl-Δ^2-oxazolin-5-one (17). A solution of **17** (0.5 g, 2 mmol) in methanol (175 mL), containing a small amount of Rose Bengal (0.01 g), was irradiated under oxygen bubbling for 0.25 h. Removal of the solvent under vacuum gave a viscous material which was fractionally crystallized from a mixture (1:1) of benzene and petroleum ether to give 0.3 g (53%) of methyl α-benzamidocinnamate (**18**), mp 139–141 °C (mmp).[19]

The mother liquor after the removal of **18** was concentrated to give a product which was recrystallized from benzene to give 0.07 g (29%) of benzamide, mp 127–128 °C (mmp).

Thermolysis of 4-Benzylidene-2-phenyl-Δ^2-oxazolin-5-one (17). A. In Refluxing Methanol. A solution of **17** (0.2 g, 0.8 mmol) in methanol (10 mL) was refluxed for 5 min and the solvent was removed under vacuum. The residual solid that was left behind was triturated with a small amount of ethanol to give 0.2 g (88%) of methyl α-benzamidocinnamate (**18**), mp 140–141 °C (mmp), after recrystallization from a mixture (1:1) of petroleum ether and benzene.

B. In Refluxing Cyclohexane. Refluxing of a cyclohexane solution of **17** (0.15 g, 0.55 mmol in 50 mL) for 10 h and workup in the usual manner gave 0.13 g (87%) of the unchanged starting material, mp 165 °C (mmp).

Photooxygenation of Methyl α-Benzamidocinnamate (18). A solution of methyl α-benzamidocinnamate (**18**) (0.26, g, 1 mmol) in methanol (175 mL), containing a small amount of Rose Bengal (0.01 g), was irradiated under oxygen bubbling for 0.75 h. Removal of the solvent under vacuum gave a viscous product which was chromatographed over silica gel. Elution with a mixture (1:4) of benzene and petroleum ether gave 0.1 g (45%) of benzoic acid, mp 121–122 °C (mmp).

No other product could be isolated from this run.

Photolysis of 4-Benzylidene-2-phenyl-Δ^2-oxazolin-5-one (17). A solution of **17** (0.6 g, 2.4 mmol) in dry benzene (450 mL) was irradiated under nitrogen bubbling for 10 h. Removal of the solvent under vacuum gave a product which was chromatographed over neutral alumina. Elution of the column with petroleum ether gave 0.2 g (31%) of α-benzamidocinnamic acid (**20**), mp 233–235 °C (mmp).[19]

Further elution of the column with a mixture of (1:1) of petroleum ether and benzene gave 0.15 g (52%) of benzamide, mp 126–128 °C (mmp).

Attempted Nickel Peroxide Oxidation of 4-Benzylidene-2-phenyl-Δ^2-oxazolin-5-one (17). A mixture of **17** (0.3 g, 1 mmol) and nickel peroxide (2 g) in dry benzene (70 mL) was stirred at room temperature for 16 h. Removal of the unchanged nickel peroxide and solvent gave 0.25 g (85%) of the unchanged starting material (**17**), mp 165 °C (mmp), after recrystallization from a mixture (1:1) of benzene and petroleum ether.

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Registry No. 3a, 28687-81-2; **3b**, 5874-61-3; **8a**, 614-28-8; **8b**, 14072-62-9; **9a**, 28687-82-3; **9b**, 71370-72-4; **16**, 642-04-6; **17**, 842-74-0; **18**, 27573-05-3; **20**, 1155-48-2; benzamide, 55-21-0; *o*-dichlorobenzene, 95-50-1; benzoic acid, 65-85-0.

(19) Buckles, R. E.; Filler, R.; Hilfman, L. *J. Org. Chem.* **1952**, *17*, 233.

Iminium Salts from α-Amino Acid Decarbonylation. Application to the Synthesis of Some 1-Azabicyclo[*x.y.*0] Systems

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Received May 30, 1979

Proline, pipecolic acid, and hexahydroazepine-2-carboxylic acid have served as starting materials for the efficient synthesis of 1-azabicyclo[3.3.0]octanes (pyrrolizidines), 1-azabicyclo[4.3.0]nonanes (indolizidines), 1-azabicyclo[4.4.0]decanes (quinolizidines), and 1-azabicyclo[5.4.0]undecanes. For each ring system, the synthesis proceeded by alkylating the cyclic α-amino acid ester with a substituted malonic ester carrying a side chain of appropriate length. Iminium ion was then generated by decarbonylation of the α-(tertiaryamino) acid. Ring closure to the fused ring system resulted from attack of the nucleophilic malonate on the newly formed electrophilic carbon of the iminium ion.

Iminium salts have served as versatile reactive synthetic intermediates[3] by virtue of their ability to yield new carbon–carbon bonds via nucleophilic attack at the highly electrophilic masked carbonyl carbon and have been used in many syntheses involving fused-ring heterocycles. Although these reactive compounds have been used in the

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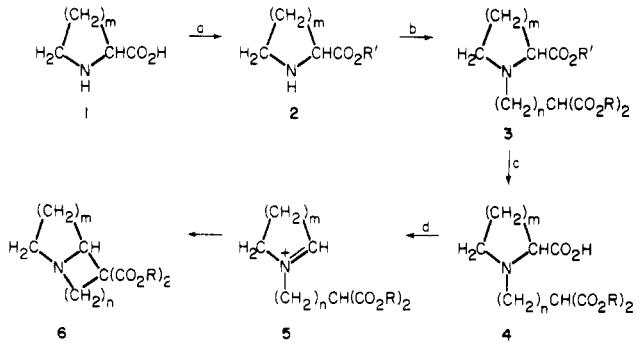
(2) Visiting Research Scholar from Seoul National University under the SNU-AID Graduate Basic Sciences Program.

(3) H. Böhme and H. G. Viehe, Ed., "Iminium Salts in Organic Chemistry", Vol. 1 and 2, Wiley-Interscience, New York, 1976 and 1978.

0022-3263/79/1944-4173$01.00/0

Scheme I



construction of alkaloids containing the 1-azabicyclo[$x.y.0$]alkane moiety, these syntheses suffer from the limitations inherent in the common procedures for generation of the necessary iminium ion intermediate such as low yield and nonregiospecificity.

We have recently reported a new iminium salt generation procedure[4] which overcomes these deficiencies. This procedure has been successfully applied to the synthesis of berbines[5] and a homotropane (anatoxin a).[6] We now wish to report the utilization of our decarbonylative iminium salt process in the preparation of various representative 1-azabicyclo[$x.y.0$] carboxylic esters.

Our basic synthetic plan has four steps as shown in Scheme I: (a) preparation of the desired cyclic α-amino acid with blocking of the carboxylic acid as an ester such that differentiation and regeneration can be subsequently effected, (b) alkylation of the secondary α-amino ester with the appropriate carbon chain containing a potential nucleophilic component, (c) deprotection of the α-amino acid carboxyl, and (d) cyclization via the regiospecifically generated iminium salt intermediate.

The 1-azabicyclo[$x.y.0$] unit was chosen as the structural feature on which to demonstrate the scope of this process since this unit is common to many natural products, with typical values for x and y ranging from 2 to 5. For examples, the senecio alkaloids are substituted pyrrolizidines or 1-azabicyclo[3.3.0]octanes, and the lupin alkaloids contain a quinolizidine or 1-azabicyclo[4.4.0]decane skeleton. Our objective has been to prepare 1-azabicyclo esters with various combinations of five-, six-, and seven-membered rings and thus to define the application of this process as a function of ring size. Our results will be presented on the basis of the size of the ring formed by cyclization into the precursor α-(tertiaryamino) acids.

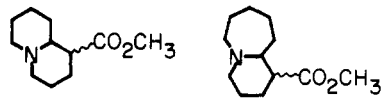
1-Azabicycles by Six-Membered Ring Formation. The syntheses began with proline (**1**, m = 2), pipecolic acid (**1**, m = 3), and hexahydroazepine-2-carboxylic acid (**1**, m = 4).[7] In all cases, the benzyl ester **2** (R' = $CH_2C_6H_5$) was used to block the amino acid carboxyl function (step a) in anticipation of its removal by catalytic hydrogenolysis.

The six-membered ring-forming precursors were all obtained by alkylation of the cyclic α-amino acid benzyl esters with diethyl 3-bromopropylmalonate[8] which provided the needed three-carbon unit plus the potential anionic center for intramolecular nucleophilic ring closure (step b). The reaction conditions typically involved use of an excess (150–200 mol %) of the alkyl bromide in benzene or benzene/DMF with anhydrous potassium carbonate as the acid scavenger and a reactant concentration of 0.3–0.4 M.

The alkylated amino ester, N-(4,4-bis(ethoxycarbonyl)-n-butyl)proline benzyl ester (**3**, m = 2; n = 3; R' = Bn; R = C_2H_5), was prepared in 89% yield by the slow addition of the amino ester **2** (m = 2; R' = Bn) to the alkyl bromide in benzene at 70 °C to avoid diketopiperazine formation. The corresponding six- and seven-membered ring compounds, benzyl N-(4,4-bis(ethoxycarbonyl)-n-butyl)pipecolate (**3**, m = 3) and benzyl N-(4,4-bis(ethoxycarbonyl)-n-butyl)hexahydroazepine-2-carboxylate (**3**, m = 4), were obtained in 87 and 72% yield, respectively. In these cases, the halide was added over a period of 10 h to a solution of the amino ester in benzene–DMF at 80 °C; heating was continued for 20 h. In all cases the initial products were analytically pure after distribution between aqueous acid and base and organic solvent and removal of volatiles under high vacuum. Catalytic hydrogenolysis of these benzyl esters over palladium on carbon in ethanol gave the free amino acids **4** (step c), usually obtained as crystalline solids after trituration with ether–hexane.

To effect the cyclization, step d, the amino acids **4** were mixed with phosphorus oxychloride and heated briefly to complete decarbonylation and form the iminium ions **5**. Addition of water and adjustment of the pH to 6–6.5 resulted in cyclization to the corresponding 1-azabicycloalkane diesters **6**. Thus, acids **1**, m = 2, **3**, and **4**, gave diethyl 1-azabicyclo[4.3.0]nonane-5,5-dicarboxylate (**6**, m = 2; n = 3), diethyl 1-azabicyclo[4.4.0]decane-5,5-dicarboxylate (**6**, m = 3; n = 3), and diethyl 1-azabicyclo[5.4.0]undecane-8,8-dicarboxylate[9] (**6**, m = 4; n = 3), respectively, in yields of 63, 75, and 77% from the corresponding benzyl esters **3**.

Diesters **6** (n = 3; m = 3; and m = 4) were heated with concentrated HCl for 24 h followed by removal of water to give the crude α-amino acid hydrochlorides. Re-esterification with methanol–HCl gave the monoesters, methyl 1-azabicyclo[4.4.0]decane-5-carboxylate (**7**) and methyl 1-azabicyclo[5.4.0]undecane-8-carboxylate (**8**). Gas chro-



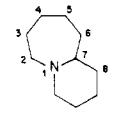
7 **8**

matography established that each sample was composed of a mixture of isomers in a ratio of 7/3 and 3/1, respectively.

1-Azabicycles by Five-Membered Ring Formation. The method used in Scheme I for the formation of 1-azabicycles via six-membered ring formation is not directly applicable to the corresponding five-membered ring case. This is because the corresponding 2-bromoethylmalonate cyclizes to the cyclopropane derivative.[10] Nucleophilic ring opening of such a cyclopropane intermediate was considered but abandoned because it was incompatible with other functionalities found in our iminium ion approach to pyrrolizidines.

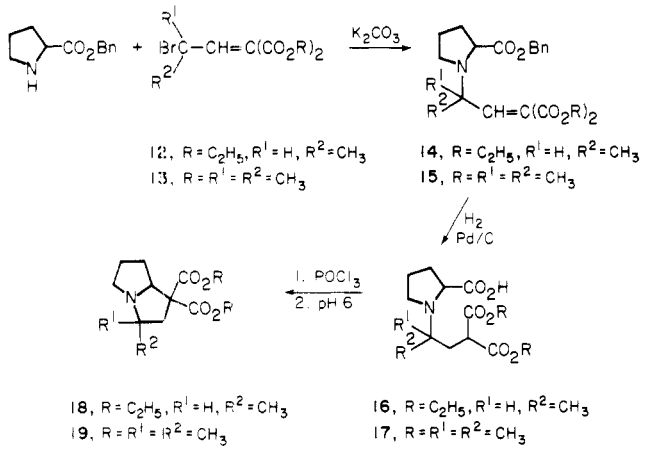
(4) R. T. Dean, H. C. Padgett, and H. Rapoport, *J. Am. Chem. Soc.* **98**, 7448 (1976).
(5) R. T. Dean and H. Rapoport, *J. Org. Chem.*, **43**, 2115, 4183 (1978).
(6) H. A. Bates and H. Rapoport, *J. Am. Chem. Soc.*, **101**, 1259 (1979).
(7) H. T. Nagasawa, J. A. Elberling, P. S. Fraser, and N. S. Mizuno, *J. Med. Chem.*, **14**, 501 (1971).
(8) F. Salmon-Legagneur, *Bull. Soc. Chim. Fr.*, 1263 (1956).

(9) Nomenclature follows the convention that numbering commences around the largest ring first regardless of substituents. Thus 1-azabicyclo[5.4.0]undecane is numbered



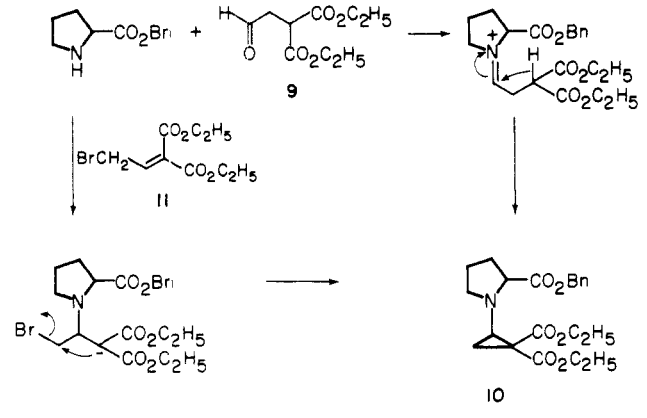
(10) A. C. Knipe and C. J. M. Stirling, *J. Chem. Soc. B*, 67 (1968).

Scheme II



Our first attempt to overcome this problem involved condensation of proline benzyl ester with the aldehydomalonate **9**,[11] in the hope that the iminium salt thus formed could be reduced to the tertiaryamino acid. This was thwarted since here again formation of cyclopropane **10** predominates.

A partial solution was found by using ethylidene malonates. Allylic bromination of diethyl ethylidenemalonate,[12] propylidenemalonate,[13] and isobutylidenemalonate[14] with NBS in each case gave the corresponding allylic bromide **11**, **12**, and **13** in good yield. Attempted alkylation of proline benzyl ester with the 2-bromoethylidemalonate **11** failed. Michael addition is the initial reaction, and this is followed by α-anion attack to displace the γ-bromide and form cyclopropane **10**.



Successful alkylation was achieved with the more branched bromides, and as expected,[14] the N-alkylated prolines **14** and **15** were the only products formed. Catalytic hydrogenation both reduced the double bond and cleaved the benzyl ester, resulting in the saturated free acids **16** and **17**. Converting to the intermediate iminium ions with phosphorus oxychloride and then allowing cyclization to proceed at pH 6 led to the 2-methyl- and 2,2-dimethyl-1-azabicyclo[3.3.0]octane 4,4-diesters, **18** and **19**, respectively (Scheme II).

A process for preparing the 2-unsubstituted pyrrolizidine **25** was then developed based on our recent blocking ester variation of the malonic ester synthesis[15] as shown in Scheme III. Proline benzyl ester was alkylated with the bromo triester **20** to afford the benzyl triethyl tetraester **21**. Selective decarbethoxylation with minimal transesterification is achieved by brief treatment with sodium benzylate in dimethyl sulfoxide (Me_2SO) to form the benzyl diethyl triester **22** which was then hydrogenolyzed to the acid diethyl ester **23**. Alternatively, the benzyl group in tetraester **21** could be removed first, yielding the acid triester **24** which was then decarbethoxylated with ethoxide.

Final ring closure to the pyrrolizidine **25**, diethyl 1-azabicyclo[3.3.0]octane-4,4-dicarboxylate, proceeded easily and well according to the general process for generating iminium ion followed by cyclization at pH 6. Considering the relatively mild and simple manipulations involved, this methodology for synthesis of pyrrolizidines shows promise in application to alkaloids containing this ring system.

1-Azabicycles by Seven-Membered Ring Formation. As in the case of the five-membered ring precursors, the procedure used to prepare the six-membered ring precursors, alkylation of the amino esters with the bromoalkylmalonate, cannot be used for the seven-membered ring precursors. The prerequisite carbon-chain alkyl halide, diethyl 4-bromobutylmalonate, does not exist as a usable intermediate, if at all,[15] because of its extremely facile cyclization to diethyl cyclopentane-1,1-dicarboxylate.[10,16] To overcome this problem, we first turned to unsaturation in the carbon chain to geometrically prevent ring formation. This approach, using 1,4-dichloro-2-butyne and proceeding through diethyl 4-chlorobutynylmalonate which was then used to alkylate benzyl and *tert*-butyl pipecolate, was partially successful. Complete hydrogenation of the triple bond and benzylic hydrogenolysis also was accompanied by significant allylic cleavage, and we lost the side chain.

We then sought to proceed throught the olefinic side chain and to obtain it by cis reduction of the triple bond. Such a cis double bond in the side chain should enhance subsequent ring formation. Reduction to the double bond was clean, but it could not be maintained during hydrogenolyses of the benzyl ester. Removal of the benzyl ester, or alternatively the *tert*-butyl ester, by acid cleavage was abandoned since it also led to partial double-bond isomerization.[15]

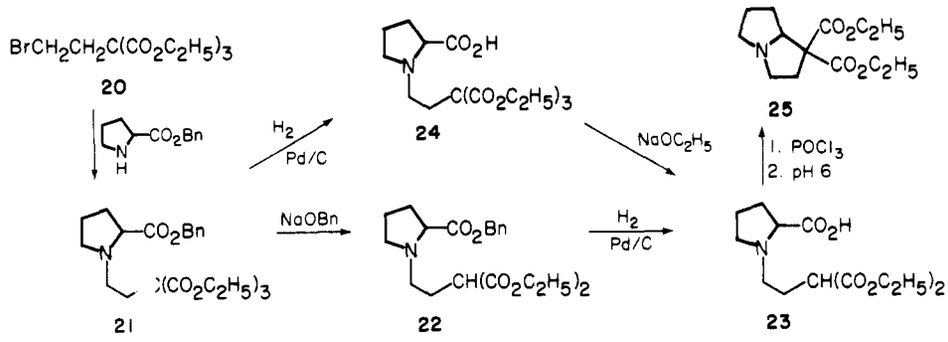
A successful route to the desired substituted pipecolic acid **26** was found using the blocking ester variation of the malonic ester synthesis. It proceeded through the triester, triethyl 5-bromopentane-1,1,1-tricarboxylate, alkylation of benzyl pipecolate, hydrogenolysis to the acid triethyl ester, and finally decarbethoxylation to the acid diester **26**.[15]

Subjecting the α-(tertiaryamino) acid **26** to the standard conditions for iminium ion formation followed by cyclization did not yield any of the 1-azabicyclo[5.4.0]undecane **29**; only polymeric material was isolated (Scheme IV). That this result was not due to any difficulty in iminium ion **27** formation was established by reduction of the intermediate and isolation of the corresponding tertiary amine **28** in 84% overall yield. An independent synthesis from piperidine and triethyl 5-bromopentane-1,1,1-tricarboxylate followed by monodecarbethoxylation gave authentic **28**.

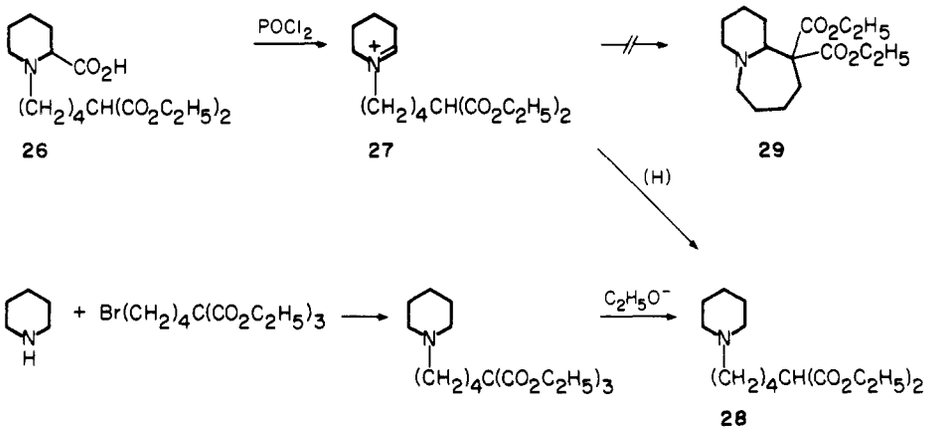
Although the seven-membered ring could not be closed on an existing six-membered ring, this 1-azabicyclo[5.4.0]-

(11) V. Franzen, *Justus Liebigs Ann. Chem.*, **623**, 68 (1959); J. Bagot, O. Siffert, and B. Millet, *Bull. Soc. Chim. Fr.* 919 (1969).
(12) W. S. Fones, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, 1963, p 293.
(13) A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941).
(14) R. Verhe, N. De Kimpe, L. De Buyk, D. Courtheyn, and N. Schamp, *Bull. Soc. Chim. Belg.*, **86**, 55 (1977).
(15) H. C. Padgett, I. G. Csendes, and H. Rapoport, *J. Org. Chem.*, in press.
(16) V. P. Golmov, *J. Gen. Chem. USSR (Engl. Transl.)* **22**, 1993 (1952).

Scheme III



Scheme IV



undecane ring system was previously prepared (6, $m = 4$; $n = 3$; R = C_2H_5) by reversing the process, that is closing a six-membered ring on an existing seven-membered ring. We have also demonstrated the efficacy of our method of ring closure for the synthesis of 1-azabicyclo[3.3.0]octanes (pyrrolizidines), 1-azabicyclo[4.3.0]nonanes (indolizidines), and 1-azabicyclo[4.4.0]decanes (quinolizidines).

Experimental Section[17]

Proline benzyl ester (2, $m = 2$; R′ = $CH_2C_6H_5$)[18] and **benzyl pipecolate** (2, $m = 3$; R′ = $CH_2C_6H_5$)[15] were prepared following procedures reported in the literature.

Benzyl Hexahydroazepine-2-carboxylate (2, $m = 4$; R′ $CH_2C_6H_5$). Hexahydroazepine-2-carboxylic acid (17.0 g, 0.12 mol), *p*-toluenesulfonic acid monohydrate (45 g, 0.24 mol, 200 mol %), benzyl alcohol (64 g, 0.60 mol, 500 mol %), and 300 mL of benzene were heated at reflux for 1.5 h, using a Dean–Stark trap to remove water. After 220 mL of benzene was removed by distillation, the reaction mixture was cooled to room tem perature, ether (400 mL) was added with stirring, and the mixture was placed in the cold overnight. The solid formed was filtered and washed with ether and hexane several times to give 37 g (77%) of colorless benzyl hexahydroazepine-2-carboxylate *p*-toluenesulfonate. Benzyl hexahydroazepine-2-carboxylate was obtained quantitatively by dissolving the salt in 10% aqueous K_2CO_3, extracting the solution twice with CH_2Cl_2, and drying and evaporating the solvent: NMR δ 1.4–2.2 (m, 9 H), 2.5–3.0 (m, 2 H), 3.2–3.6 (m, 1 H), 5.0 (s, 2 H), 7.2 (s, 5 H); IR 3000, 1740, 1450 1160 cm^{-1}. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.1; H, 8.2; N, 6.0. Found: C, 71.9; H, 8.1; N, 6.2.

(17) All solvents were dried over $MgSO_4$ prior to evaporation in vacuo, using a Berkeley rotary evaporator. NMR spectra were determined in $CDCl_3$ solution, using internal Me_4Si, and IR spectra were recorded for liquid films unless otherwise indicated. Melting points are uncorrected. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley, Calif.

(18) J. Ramachandran and Cho-Hao Li, *J. Org. Chem.*, 28, 173 (1963).

***N*-(4,4-Bis(ethoxycarbonyl)-*n*-butyl)proline Benzyl Ester (3, $m = 2$; $n = 3$; R = C_2H_5; R′ = $CH_2C_6H_5$).** A solution of 9.19 g (44.8 mmol) of proline benzyl ester in 30 mL of benzene was added via syringe pump over a period of 10 h to a stirred mixture of diethyl 3-bromopropylmalonate[8] (18.9 g, 67.2 mmol) and anhydrous K_2CO_3 (19.3 g, 0.14 mol) in 90 mL of benzene at 70 °C under nitrogen. After the addition was completed, the mixture was heated at 70 °C for 72 h and poured into 200 mL of water, and the organic layer was separated. The aqueous layer was extracted with ether, the combined organic layers were extracted with 1 M phosphoric acid, the acidic aqueous layer was made alkaline with potassium carbonate, and the alkaline aqueous phase was extracted several times with methylene chloride. The organic extracts were dried, the solvent was evaporated, and low boiling impurities were removed at 100 °C under high vacuum (0.02 mm) to give 16.1 g (89%) of a colorless oil: NMR δ 1.20 (t, 6 H, J = 7 Hz), 1.50–2.95 (m, 9 H), 3.00–3.50 (m, 5 H), 4.20 (q, 4 H, J = 7 Hz), 5.17 (s, 2 H), 7.33 (s, 5 H); IR 3050, 2900, 1730, 1450, 1360, 1150, 750 cm^{-1}. Anal. Calcd for $C_{22}H_{31}NO_6$: C, 65.2; H, 7.7; N, 3.4. Found: C, 65.1; H, 7.7; N, 3.4.

Benzyl *N*-(4,4-bis(ethoxycarbonyl)-*n*-butyl)pipecolate (3, $m = 3$; $n = 3$; R = C_2H_5, R′ = $CH_2C_6H_5$) and benzyl *N*-(4,4-bis(ethoxycarbonyl)-*n*-butyl)hexahydroazepine-2-carboxylate (3, $m = 4$; $n = 3$; R = C_2H_5, R′ = $CH_2C_6H_5$) were prepared by the same procedure as above except that the solvent was benzene–DMF, 1/1, and heating was carried out for 20 h at 80 °C.

Benzyl *N*-(4,4-bis(ethoxycarbonyl)-*n*-butyl)pipecolate: 87% yield; NMR δ 1.0–3.5 (m, 22 H), 4.2 (q, 4 H), 5.05 (s, 2 H), 7.3 (s, 5 H); IR 2980, 1730, 1440, 1360, 1140 cm^{-1}. Anal. Calcd for $C_{23}H_{33}NO_6$: C, 65.8; H, 7.9; N, 3.3. Found: C, 65.6; H, 7.6; N, 3.4.

Benzyl *N*-(4,4-bis(ethoxycarbonyl)-*n*-butyl)hexahydroazepine-2-carboxylate: 72% yield; NMR δ 1.0–2.1 (m, 17 H), 2.2–3.6 (m, 7 H), 4.1 (q, 4 H), 5.05 (s, 2 H), 7.25 (s, 5 H); IR 3000, 1730, 1445, 1360, 1160 cm^{-1}. Anal. Calcd for $C_{24}H_{35}NO_6$: C, 66.5; H, 8.1; N, 3.2. Found: C, 66.4; H, 8.1; N, 3.4.

Hydrogenolysis of Benzyl Esters 3 to Acids 4. Catalytic hydrogenation of the amino esters in ethanol over 10% by weight of 10% Pd/C in a Parr apparatus at 45 psi was allowed to proceed

for 20 h. After filtration and washing of the catalyst and evaporation of the solvent, the pure amino acids were obtained.

***N*-(4,4-Bis(ethoxycarbonyl)-*n*-butyl)proline (4, *m* = 2; *n* = 3; R = C_2H_5)**: 84% yield as a foam used further without purification; NMR δ 1.25 (t, 6 H, *J* = 6 Hz), 1.65–2.50 (m, 7 *H*), 3.00–4.00 (m, 7 H), 4.20 (q, 4 H, *J* = 7 Hz), 6.50 (br, 1 H); IR 3400, 3000, 2900, 1750–1725, 1600 cm^{-1}. ***N*-(4,4-Bis(ethoxycarbonyl)-*n*-butyl)pipecolic acid (4, *m* = 3; *n* = 3; R = C_2H_5)**: 89% yield; mp 132–134 °C after trituration with hexane–ether (1/4); NMR δ 1.1–3.8 (m, 22 H), 4.2 (q, 4 H); IR (Nujol) 3000, 1740, 1630, 1460, 1370, 1170 cm^{-1}. Anal. Calcd for $C_{16}H_{27}NO_6$: C, 58.3; H, 8.3; N, 4.3. Found: C, 58.4; H, 8.3; N, 4.3.

***N*-(4,4-Bis(ethoxycarbonyl)-*n*-butyl)hexahydroazepine-2-carboxylic acid (4, *m* = 4; *n* = 3; R = C_2H_5)**: 92% yield; mp 99–101 °C after trituration with hexane–ether (1/4); NMR δ 1.2 (t, 6 H), 1.4–2.4 (m, 12 H), 2.8–3.8 (m, 6 H), 4.2 (q, 4 H); IR (KBr) 3600, 3000, 1760, 1730, 1630, 1325 cm^{-1}. Anal. Calcd for $C_{17}H_{29}NO_6$: C, 59.4; H, 8.5; N, 4.1. Found: C, 59.4; H, 8.5; N, 4.1.

Cyclizations of Acid Diesters 4 with Six-Membered Ring Formation to 6. The amino acid (4, 100 mol %) was mixed with phosphorus oxychloride (1000 mol %, freshly distilled), and the flask was immersed in a 100 °C bath with stirring. The decarbonylation proceeded vigorously and was complete in 3–4 min, as verified by IR. The mixture was cooled in ice–water, and water was then added slowly with stirring to form a solution approximately 0.05 M in iminium ion. Potassium carbonate was added to pH 6–6.5, and the solution was allowed to sit at room temperature overnight. It was then cooled, brought to pH 9–10 with K_2CO_3, and extracted with ether. The ether was washed, dried, and evaporated, yielding the crude product, which was subjected to Kugelrohr distillation to give the pure cyclized product.

Diethyl 1-azabicyclo[4.3.0]nonane-5,5-dicarboxylate (1,1-bis(ethoxycarbonyl)indolizidine (6), *m* = 2; *n* = 3; *R* = C_2H_5): bp 75 °C (0.1 mm); 63% yield; NMR δ 1.25 (2 t, 6 H, *J* = 7 Hz), 1.40–2.65 (m, 11 H), 3.05 (m, 2 H), 4.20 (2 q, 4 H, *J* = 7 Hz); IR 3000, 2900, 1735 cm^{-1}; MS *m/e* 269 (M^+). Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.4; H, 8.6; N, 5.2. Found: C, 62.3; H, 8.6; N, 5.2.

Diethyl 1-azabicyclo[4.4.0]decane-5,5-dicarboxylate (1,1-bis(ethoxycarbonyl)quinolizidine (6), *m* = 3; *n* = 3; R = C_2H_5): bp 90–95 °C (0.05 mm); 74% yield; NMR δ 1.1–3.2 (m, 21 H), 4.15 (double quartets, 4 H); IR 3000, 2820, 2750, 1730, 1440, 1360, 1240, 1030 cm^{-1}. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.6; H, 8.9; N, 4.9. Found: C, 63.5; H, 8.8; N, 5.0.

Diethyl 1-azabicyclo[5.4.0]undecane-8,8-dicarboxylate (6 *m* = 4; *n* = 3; R = C_2H_5): bp 105 C (0.1 mm); 78% yield; NMR (CCl_4) δ 1.1–2.1 (m, 18 H), 2.45–3.25 (m, 5 H), 4.2 (q, 4 H); IR 2930, 1730, 1440, 1250 cm^{-1}. Anal. Calcd for $C_{16}H_{27}NO_4$: C, 64.6; H, 9.1; N, 4.7. Found: C, 64.8; H, 9.1; N, 4.7.

Methyl 1-Azabicyclo[4.4.0]decane-5-carboxylate (7). Diethyl 1-azabicyclo[4.4.0]decane-5,5-dicarboxylate was heated at reflux in 6 N HCl for 19 h. After evaporation of the water, dry methanol was added to the residue and dry HCl gas was bubbled in for 10 min. The mixture was refluxed for 3 h then cooled and brought to pH 9–10 in the cold after addition of water. The resulting mixture was extracted with ether and washed, dried, and evaporated to give an oil which was Kugelrohr distilled, bp 58–60 °C (0.1 mm). Gas chromatography using a 10-ft 10% OV-17 column at 230 °C with a He flow of 60 mL/min showed the existence of methyl lupinate and methyl epilupinate in a ratio of 7/3: IR 2900, 2780, 2710, 1730, 1435, 1140 cm^{-1}; NMR (CCl_4) δ 0.9–2.95 (m, 16 H), 3.6 (s, 3 H). Anal. Calcd for $C_{11}H_{19}NO_2$: C, 67.0; H, 9.7; N, 7.1. Found: C, 66.7; H, 9.7; N, 7.1.

Methyl 1-azabicyclo[5.4.0]undecane-8-carboxylate (8) was prepared as above from diethyl 1-azabicyclo[5.4.0]undecane-8,8-dicarboxylate by hydrolysis, decarboxylation, and re-esterification in 71% yield: bp 70 °C (0.1 mm); GC as above, 2 peaks, ratio 3/1; NMR (CCl_4) δ 1.35–1.95 (broad s, 12 H), 2.0–3.0 (m, 6 H), 3.6 (s, 3 H); IR 2910, 1730, 1430, 1150 cm^{-1}. Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.2; H, 10.0; N, 6.6. Found: C, 68.0; H, 9.9; N, 6.6.

***N*-(1-Methyl-3,3-bis(ethoxycarbonyl)-2-propenyl)proline Benzyl Ester (14).** A solution of 1.80 g (8.80 mmol) of benzyl proline in 3 mL of anhydrous ether was added via syringe pump over a period of 3 h to a stirred solution of 1.22 g (4.40 mmol) of diethyl 2-bromopropylidenemalonate (12)[13] in 5 mL of anhydrous ether. Precipitation of benzyl proline hydrobromide began immediately. The mixture was refluxed under nitrogen for 5 h, poured into water, and extracted with ether. The combined ether phase was dried, and the solvent was evaporated to give 2.10 g of crude 14, which after chromatography on silica gel (chloroform–acetone, 97/3) afforded 1.06 g (64%) of pure 14: NMR (CCl_4) δ 1.2 (m, 9 H), 1.85 (m, 4 H), 2.5–3.1 (m, 2 H), 3.2–3.8 (m, 2 H), 4.15 (2 q, 4 H), 5.0 (s, 2 H), 6.75 (d, 1 H), 7.25 (s, 5 H); IR 3550, 3050, 1725, 1650, 1450, 740 cm^{-1}. Anal. Calcd for $C_{22}H_{29}NO_6$: C, 65.5; H, 7.2; N, 3.5. Found: C, 65.3; H, 7.2; N, 3.4.

***N*-(1,1-Dimethyl-3,3-bis(methoxycarbonyl)-2-propenyl)proline benzyl ester (15)** was prepared in the same way as 14, except that dimethyl 2-bromoisobutylidenemalonate (13)[14] was used as the alkylating agent: NMR (CCl_4) δ 1.2 (2 s, 6 H), 1.9 (m, 4 H), 2.3–3.3 (m, 2 H), 3.6 (m, 1 H), 3.65 (s, 6 H), 5.0 (s, 2 H), 6.7 (s, 1 H), 7.2 (s, 5 H); IR 3000, 1725, 1665, 1450, 740 cm^{-1}; MS *m/e* 389 (M^+).

***N*-(1-Methyl-3,3-bis(ethoxycarbonyl)-*n*-propyl)proline (16).** To 0.35 g (0.87 mmol) of 14 dissolved in 10 mL of 95% ethanol and placed in a 25 mL Parr hydrogenation bottle was added 75 mg of 10% Pd/C, and the mixture was hydrogenated at 42 psi for 18 h. The catalyst was removed by filtration and the solvent evaporated to give 250 mg (92%) of a viscous oil which was used without further purification: NMR δ 1.27 (t, 9 H), 1.80–2.50 (br, 6 H), 3.0–4.0 (m, 5 H), 4.17 (q, 4 H), 9.05 (br, 1 H); IR 3400, 3000, 1730, 1640 cm^{-1}.

***N*-(1,1-Dimethyl-3,3-bis(methoxycarbonyl)-*n*-propyl)-proline (17)** was prepared in the same manner as 16, and 0.425 g of 15 gave 0.310 g (93%) of 17: NMR δ 1.00–1.40 (m, 2 H), 1.27 (s, 6 H), 1.67–2.50 (m, 6 H), 3.40–3.80 (m, 3 H), 3.73 (s, 3 H), 3.77 (s, 3 H), 5.90 (br, 1 H); IR 3400, 2950, 1720, 1640 cm^{-1}.

2-Methyl-4,4-bis(ethoxycarbonyl)pyrrolizidine (Diethyl 2-Methyl-1-azabicyclo[3.3.0]octane-4,4-dicarboxylate, 18). To 0.163 g (0.52 mmol) of 16 was added 0.77 g (5 mmol) of phosphorus oxychloride, and the solution was immersed in a 100 °C oil bath for 3 min. The reaction mixture was rapidly cooled, 6 mL of ice water was added, and the pH was adjusted to 6, using potassium carbonate. After standing at room temperature for 16 h, the mixture was saturated with potassium carbonate and extracted with ether. The ether extracts were washed with water and dried, and the solvent was evaporated to give 0.089 g of crude 18 which was further purified by Kugelrohr distillation to afford 0.072 g (51%) of the pure pyrrolizidine 18: NMR (CCl_4) δ 1.0 (d, 3 H, *J* = 6 Hz), 1.2 (t, 6 H, *J* = 7 Hz), 1.58–2.00 (m, 6 H), 2.20–3.15 (m, 4 H), 4.17 (q, 4 H, *J* = 7 Hz); MS *m/e* 269 (M^+). Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.4; H, 8.6; N, 5.2. Found: C, 62.3; H, 8.6; N, 5.0.

2,2-Dimethyl-4,4-bis(methoxycarbonyl)pyrrolizidine (dimethyl 2,2-dimethyl-1-azabicyclo[3.3.0]octane-4,4-dicarboxylate, 19) was prepared in the same way as 18, and 146 mg of 17 gave 51 mg (41%) of 19: ^1H NMR δ 1.03 (s, 3 H), 1.25 (s, 3 H), 1.60–2.35 (m, 5 H), 2.60–3.10 (m, 3 H), 3.67 (s, 3 H), 3.72 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.07, 171.96, 69.08, 65.39, 61.17, 52.73, 52.48, 47.87, 45.49, 29.08, 27.73, 25.53, 25.45; MS *m/e* 255 (M^+). Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.2; H, 8.3; N, 5.5. Found: C, 61.0; H, 8.2; N, 5.3.

***N*-(3,3,3-Tris(ethoxycarbonyl)-*n*-propyl)proline Benzyl Ester (21).** A mixture of 1.37 g (6.68 mmol) of proline benzyl ester and 2.80 g (20 mmol) of potassium carbonate in 12 mL of benzene–DMF, 1/1, was stirred and heated at 80 °C under nitrogen. A solution of 3.12 g (10 mmol) of bromo triester **20**[15] in 3 mL of benzene–DMF, 1/1, was added during 30 min, and the mixture was heated at 80 °C for 20 h. The mixture was cooled and diluted with benzene, the inorganic residue filtered off, and DMF removed by several water washes. The organic phase was dried, the solvent evaporated, and the residue of 3.12 g chromatographed on silica gel (benzene–ethyl acetate, 4/1) to give 1.08 g (35%) of the tetraester 21: NMR δ 1.25 (t, 9 H, *J* = 7 Hz), 1.9 (m, 4 H), 2.2–3.4 (m, 7 H), 4.25 (q, 6 H, *J* = 7 Hz), 5.2 (s, 2 H), 7.3 (s, 5 H); IR 3500, 3000, 1730, 1450, 740, 690 cm^{-1}; MS *m/e* 418 ($M^+ - OC_2H_5$), 390 ($M^+ - CO_2C_2H_5$). Anal. Calcd for $C_{24}H_{33}NO_3$: C, 62.2; H, 7.2; N, 3.0. Found: C, 62.2; H, 7.1; N, 2.9.

***N*-(3,3-Bis(ethoxycarbonyl)-*n*-propyl)proline Benzyl Ester (22).** To a stirred suspension of 0.20 g (1.54 mmol) of sodium

benzylate in 10 mL of anhydrous dimethyl sulfoxide was added 0.50 g (1.08 mmol) of tetraester **21**. After the mixture had been stirred for 10 min at room temperature, a clear solution was formed. The mixture was stirred for 5 more min, diluted with benzene, and extracted several times with 1 M phosphoric acid. The acidic aqueous phase was made alkaline with potassium carbonate and extracted with benzene, and the organic phase was washed with saturated sodium chloride solution, dried, and evaporated to give 0.345 g of a yellow oil. Preparative TLC (benzene–ethyl acetate, 3/2) gave 0.32 g (75%) of the benzyl diethyl triester **22**: NMR (CCl_4) δ 1.25 (t, 6 H, J = 7 Hz), 1.70–2.20 (m, 5 H), 2.25–3.55 (m, 7 H), 4.10 (q, 4 H, J = 7 Hz), 5.00 (s, 2 H), 7.20 (s, 5 H); IR 3000, 1730, 1430, 735, 680 cm^{-1}; MS m/e 346 ($M^+ - OC_2H_5$), 318 ($M^+ - CO_2C_2H_5$).

***N*-(3,3-Bis(ethoxycarbonyl)-*n*-propyl)proline (23).** To 0.50 g (1.28 mmol) of *N*-(3,3-bis(ethoxycarbonyl)-*n*-propyl)proline benzyl ester (**22**) dissolved in 25 mL of absolute ethanol was added 60 mg of 10% Pd/C. The mixture was hydrogenated at 50 psi for 18 h, the catalyst was removed, and the solvent was evaporated to give 350 mg (90%) of **23**, which was used without further purification: NMR δ 1.3 (t, 6 H, J = 6 Hz), 1.8–2.6 (m, 6 H), 2.65–4.40 (m, 10 H), 8.9 (br, 1 H).

4,4-Bis(ethoxycarbonyl)pyrrolizidine (Diethyl 1-Azabicyclo[3.3.0]octane-4,4-dicarboxylate, 25). To 0.10 g (0.33 mmol) of *N*-(3,3-bis(ethoxycarbonyl)-*n*-propyl)proline (**23**) was added 0.52 g (3.30 mmol) of phosphorus oxychloride, and the mixture was heated at 100 °C for 2 min. After the solution was cooled, 10 mL of ice water was added, and the pH was adjusted to 6.0 with potassium carbonate, the mixture was left at room temperature for 6 h, then it was saturated with potassium carbonate and extracted with ether. The ether layer was dried, the solvent evaporated, and the residue Kugelrohr distilled, yielding 0.048 g (57%) of pure **25**: NMR δ 1.20 (t, 6 H, J = 7 Hz), 1.60–3.30 (m, 11 H), 4.15 (q, 4 H, J = 7 Hz); IR 3000, 1730, 1250 cm^{-1}; MS m/e 255 (M^+). Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.2; H, 8.3; N, 5.5. Found: C, 61.1; H, 8.3; N, 5.3.

Formation of iminium ion 27 was carried out from 1.13 g (3.3 mmol) of *N*-(5,5-bis(ethoxycarbonyl)-*n*-pentyl)pipecolic acid (**26**) by adding phosphorus oxychloride (3.2 mL, freshly distilled) and heating and stirring for 4 min. Treatment in the usual way for cyclization led only to polymeric material; none of the 1-azabicyclo[5.4.0]undecane diester **29** could be isolated.

An identical decarbonylation reaction mixture was cooled, and 50 mL of ice–water was added, followed by sodium bicarbonate to pH 4 and 0.5 g of 10% Pd/C. After hydrogenation at 40 psi for 2 h, the solution was filtered, and the filtrate was made alkaline with potassium carbonate and extracted with ether. The ether was washed with water and saturated NaCl, dried, and evaporated to give ***N*-(5,5-bis(ethoxycarbonyl)-*n*-pentyl)piperidine (28)**: 0.84 g; 2.8 mmol; 85%; identical by NMR, IR, and GC with an authentic sample prepared below.

***N*-(5,5,5-Tris(ethoxycarbonyl)-*n*-pentyl)piperidine.** Piperidine (2.3 g, 27 mmol), triethyl 5-bromopentane-1,1,1-tricarboxylate (5 g, 13.5 mmol), and benzene (50 mL) were mixed and placed at room temperature for 24 h. The piperidine hydrobromide was filtered off, and the filtrate was extracted several times with cold 1 M H_3PO_4. The cold acid solution was adjusted to pH 10 with K_2CO_3 and then extracted with ether. Drying and evaporating the ether left an oil weighing 2.5 g (6.7 mmol; 50% yield): NMR δ 1.0–1.8 (m, 19 H), 1.9–2.6 (m, 8 H), 4.2 (q, 6 H); IR 3000, 1760, 1750, 1250 cm^{-1}. Anal. Calcd for $C_{19}H_{33}NO_6$: C, 61.4; H, 8.9; N, 3.8. Found: C, 61.2; H, 8.8; N, 3.8.

***N*-(5,5-Bis(ethoxycarbonyl)-*n*-pentyl)piperidine (28).** *N*-(5,5,5-Tris(ethoxycarbonyl)-*n*-pentyl)piperidine (1.0 g, 2.7 mmol) was added to a solution of sodium metal (0.12 g, 5.25 mmol) in absolute ethanol (10 mL) at room temperature. After 15 min of stirring, the solution was cooled and cold 1 N HCl was added to pH 2. The reaction mixture was washed with ether, adjusted to pH 10 with K_2CO_3 in the cold, and again extracted with ether which was washed with water and saturated NaCl and dried. Evaporation of the ether left analytically pure diester **28**, one peak by GC: NMR δ 1.1–2.2 (m, 18 H), 2.2–2.6 (m, 6 H), 3.3 (t, 1 H), 4.2 (q, 4 H); IR 3000, 1750, 1730, 1360, 1140 cm^{-1}. Anal. Calcd for $C_{16}H_{29}NO_4$: C, 64.2; H, 9.8; N, 4.7. Found: C, 63.9; H, 9.8; N, 4.7.

Registry No. **1** (m = 4), 5227-53-2; **2** (m = 4; R′ = $CH_2C_6H_5$), 61212-37-1; **2** (m = 2; R′ = $CH_2C_6H_5$), 41324-66-7; **2** (m = 3; R′ = $CH_2C_6H_5$), 38068-75-6; **2** (m = 4; R′ = *p*-toluenesulfonate), 71519-04-5; **3** (m = 2; n = 3; R = C_2H_5; R′ = $CH_2C_6H_5$), 71519-05-6; **3** (m = 3; n = 3; R = C_2H_5; R′ = $CH_2C_6H_5$), 71519-06-7; **3** (m = 4; n = 3; R = C_2H_5; R′ = $CH_2C_6H_5$), 61212-38-2; **4** (m = 2; n = 3; R = C_2H_5), 71519-07-8; **4** (m = 3; n = 3; R = C_2H_5), 71519-08-9; **4** (m = 4; n = 3; R = C_2H_5), 61212-39-3; **6** (m = 2; n = 3; R = C_2H_5), 71519-09-0; **6** (m = 3; n = 3; R = C_2H_5), 25647-44-3; **6** (m = 4; n = 3; R = C_2H_5), 61212-41-7; **7**, 31436-28-9; **8**, 71519-10-3; **12**, 69305-74-4; **13**, 36825-10-2; **14**, 71519-11-4; **15**, 71519-12-5; **16**, 71519-13-6; **17**, 71519-14-7; **18**, 71519-15-8; **19**, 71519-16-9; **20**, 71170-82-6; **21**, 71519-17-0; **22**, 71519-18-1; **23**, 71519-19-2; **24**, 71519-20-5; **25**, 71519-21-6; **26**, 71519-22-7; **27**, 71519-23-8; **28**, 71519-24-9; *N*-[5,5,5-tris(ethoxycarbonyl)-*n*-pentyl]piperidine, 71519-25-0; diethyl 3-bromopropylmalonate, 10149-21-0; piperidine, 110-89-4; triethyl 5-bromopentane-1,1,1-tricarboxylate, 71170-83-7.

"K-Region" Imines of Some Carcinogenic Aromatic Hydrocarbons

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A general synthesis of unsubstituted K-region arene imines from the corresponding arene oxides is described. Reaction of sodium azide with oxiranes gave mixtures of trans azido alcohols, which upon treatment with tri-*n*-butylphosphine yielded the expected arene imines. By this method the K-imines of benz[*a*]anthracene, 7-methlbenz[*a*]anthracene, dibenz[*a*,*h*]anthracene, and benzo[*a*]pyrene were prepared, and means were provided to examine the hypothesis that imines may serve as activated carcinogenic intermediates. The azido alcohols of 7,12-dimethylbenz[*a*]anthracene 5,6-oxide and of benzo[*c*]phenanthrene 5,6-oxide reacted with triisopropylphosphine to give isolable Staudinger adducts which, however, could not be converted into cyclic imines.

Recently[3] we postulated a theory that arene imines[4] are possible transformation products of polycyclic aromatic hydrocarbons in vivo. When an arene oxide alkylates an amino or nucleic acid molecule at a nitrogen atom, and the adduct is dealkylated, cyclyzation of the amino alcohol

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(4) In this context we define an arene imine as an *aziridine* structure fused to a benzene ring.

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