[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY AND THE U. S. AIR FORCE RADIATION LABORATORY, THE UNIVERSITY OF CHICAGO, CHICAGO 37, ILL.]

A New Synthesis of Aziridines[1]

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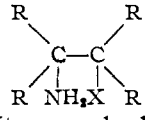
A novel synthetic route to the hitherto unknown 2,2,3,3-tetraalkylaziridines (I) has been developed. The three-step synthesis involves the chloronitrosation of a fully substituted aliphatic or alicyclic olefin, reduction of the nitroso chloride to the chloroamine derivative, and finally cyclization of the latter with alkali to the desired 2,2,3,3-tetraalkylaziridine (I). Five alkenes were converted in excellent yields to the imine analogs which were assayed for purity by gas chromatography and characterized by determination of the infrared absorption spectra, nuclear magnetic resonance spectra and elemental analyses.

Introduction

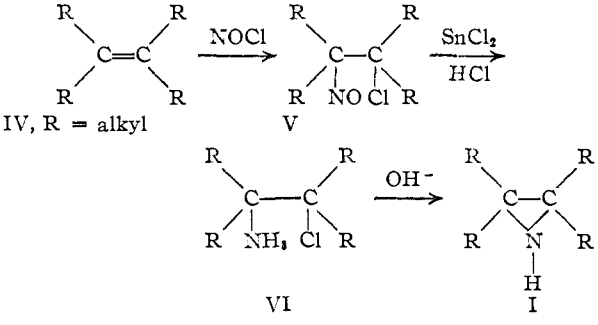
In connection with a kinetic study, a synthetic pathway to the previously unknown 2,2,3,3-tetraalkylaziridines (I) was sought. Therefore, a thorough evaluation of the known preparative methods for aziridines was made. Initially, an extension of the Hoch–Campbell synthesis[3a-g] of arylaziridines to alkylsubstituted imines was considered as a possible route to the fully substituted aziridine (I). However, preliminary work revealed that the reaction of two typical alkyl ketoximes, namely acetone and 2-butanone oxime, failed to produce aziridine derivatives and accordingly this synthetic approach was abandoned. The possibility of deriving the tetrasubstituted imine from a 1,1,2,2-tetraalkyl-2-amino-1-ethanol (II) employing the Wenker procedure[4] was only remotely considered in light of the acid-catalyzed pinacol rearrangement of tetramethyl-2-aminoethanol (IIa)[5] and the selective dehydration of 2-methyl-1-amino-2-propanol by aqueous sulfuric acid to form 2-methylallylamine in good yield.[6]



II, X = –OH, R = alkyl
III, X = –Cl, R = alkyl
IIa, R = CH_3–, X = OH

It seemed plausible to us that the cyclization of 1,1,2,2-tetraalkyl-2-chloro-1-ethylamines (III) would be an expedient route to the desired fully substituted ethylenimine analogs (I). The idea of deriving the chloroamine precursor III from the corresponding amino alcohol II was dismissed on the basis of the very poor and variable yields reported for the conversion of 1,1-diphenyl-2-amino-2-methylpropanol to 1-chloro-1,1-diphenyl-2-amino-2-methylpropane *via* thionyl chloride.[7] The extreme difficulty in transforming tertiary amino alcohols to the related chloroamines has also been noted in several other instances.[3f,6,8] Consequently, we directed our attention to the development of a simple and convenient synthetic pathway to the chloroamine III which could then be cyclized to I.

A three-step reaction sequence involving the chloronitrosation of a tetraalkylethylene (IV), reduction of the nitroso chloride V to the chloroamine hydrochloride VI, and finally ring closure of VI with alkali was utilized for the synthesis of five 2,2,3,3-tetraalkylaziridines in excellent yield.



IV, R = alkyl

Results and Discussion

The chloronitrosation of 2,3-dimethyl-2-butene (IV, R = CH_3) as a typical example, proceeded in a facile manner at $-70°$ in methanol to produce the blue, monomeric nitroso chloride (V, R = Me) in quantitative yield. Examination of the literature revealed that in a considerable number of cases,[9a-n] the reduction of aliphatic nitroso compounds proceeds in very poor yields and no convincing proof exists that the main product of the reduction is the corresponding amine. Nevertheless, we conducted a systematic evaluation of a variety of reducing agents which included $LiAlH_4$, $NaBH_4$, aluminum amalgam, Zn–acetic acid, Zn–HCl and $SnCl_2$–HCl and discovered that the latter reagent was uniquely effective for the re-

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(2) This paper comprises a portion of the dissertation submitted by S. J. B. in partial fulfillment of the requirements for the Ph.D. in the Graduate School of the University of Chicago.

(3) (a) J. Hoch, *Compt. rend.*, **198**, 1865 (1934); (b) **203**, 799 (1936); (c) **204**, 358 (1937); (d) K. N. Campbell and J. F. McKenna, *J. Org. Chem.*, **4**, 198 (1939); (e) K. N. Campbell, B. K. Campbell and E. P. Chaput, *ibid.*, **8**, 99 (1943); (f) K. N. Campbell, B. K. Campbell, J. F. McKenna and E. P. Chaput, *ibid.*, **8**, 103 (1943); (g) K. N. Campbell, B. K. Campbell, L. G. Hess and I. J. Schaffner, *ibid.*, **9**, 184 (1944).

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(5) K. A. Adams, Ph.D. Dissertation, University of Chicago, 1932; P. J. Ehman, Ph.D. Dissertation, University of Chicago, 1935.

(6) R. Adams and T. L. Cairns, THIS JOURNAL, **61**, 2464 (1939).

(7) H. M. Kissman, D. S. Tarbell and J. Williams, *ibid.*, **75**, 2959 (1953).

(8) T. W. J. Taylor, J. S. Owen and D. Whittaker, *J. Chem. Soc.*, 206 (1939).

(9) (a) A. Baeyer, *Ber.*, **28**, 2292 (1895); (b) G. Cusmane, *C. A.*, **12**, 1183 (1918); (c) N. J. Demjanow, *Ber.*, **40**, 245 (1907); (d) N. J. Demjanow, *Chem. Zentr.*, **70**, 1064 (1899); (e) J. C. Earl and J. Kenner, *J. Chem. Soc.*, 2142 (1927); (f) M. Gomberg, *Ann.*, **300**, 79 (1898); (g) A. Hantzsch, *Ber.*, **35**, 2979, 4120 (1902); (h) J. Schmidt, *ibid.*, **35**, 2329, 3728, 3733 (1902); (i) **36**, 1766 (1903); (j) J. Schmidt and P. Austin, *ibid.*, **36**, 1772 (1903); (k) J. Schmidt and F. Leipprand, *ibid.*, **37**, 537, 546 (1904); (l) J. Schmidt and K. Widmann, *ibid.*, **42**, 497, 1893 (1909); (m) J. Schmidt and H. Dieterle, *Ann.*, **377**, 48 (1910); (n) P. Tonnies, *Ber.*, **12**, 169 (1879); (p) J. G. Aston, D. F. Menard and M. G. Mayberry, THIS JOURNAL, **54**, 1530 (1932).

duction of the nitroso chloride V to the chloramine analog VI at 50–60°.[10a] The chloroamine was not isolated but directly treated with four equivalents of aqueous sodium hydroxide to bring about ring closure.[10b] Fractional Distillation of the basic product afforded a 79% yield (based on the olefin) of 2,2,3,3-tetramethylaziridine (I, R = CH_3) assayed as >98% pure by gas chromatography. The infrared spectrum of the product gave no evidence of unsaturation, but disclosed an N–H stretching frequency at 3200 cm.$^{-1}$ which appeared to be characteristic for a series of eleven other aziridine derivatives. The n.m.r. spectrum of the tetramethyl-substituted imine showed a single, sharp resonance line at 217 c.p.s. (relative to external benzene at 40 mc.) thus revealing the equivalency of the four methyl groups. This spectral evidence combined with elemental analysis, physical properties and reactivity[11] of the product present a decisive argument in favor of the aziridine structure.

The general utility of the new method was demonstrated by the conversion of 2,3-dimethyl-2-pentene, 2,3-dimethyl-2-hexene, 1,2-dimethylcyclopentene and 1,2-dimethylcyclohexene to the corresponding imines in yields ranging from 71 to 84% over-all. It is noteworthy that the bicyclic aziridines, 1,2-dimethylcyclopentenimine (1,5-dimethyl-6-azabicyclo[3.1.0]hexane) and 1,2-dimethylcyclohexenimine (1,6-dimethyl-7-azabicyclo[4.1.0]heptane), disclosed the N–H stretching vibration at a slightly shifted frequency (3225 cm.$^{-1}$)[12] perhaps due to greater internal strain inherent in these bicyclic systems.

The facile conversion of fully substituted alkenes to the related tetraalkylaziridines prompted us to explore the possibility of extending this synthetic procedure to tri-, di-, and mono-substituted olefins. Accordingly, the nitroso chlorides of 2-methyl-2-butene, 2-methyl-1-butene and cyclohexene were prepared in good yields; several attempts to chloronitrosate the mono-substituted olefin, 1-pentene, however, proved fruitless. Although an extensive study on the stannous chloride reduction of this series of nitroso compounds was carried out under a variety of experimental conditions, the conversion of the nitroso chlorides to the corresponding ethylenimine analogs could not be accomplished. The failure to isolate cyclic imine products in these instances could be ascribed to the decomposition of the nitroso compounds during reduction. The fact that the reduction of the nitroso chloride of 2-methyl-2-butene with a variety of reducing agents[9l,9k] produces ammonia in every case lends support to this hypothesis.

Acknowledgment.—We are deeply indebted to Professor Kenneth P. DuBois, Director of the U. S. Air Force Radiation Laboratory, whose interest and kind coöperation has made this investigation possible.

Experimental[13]

Preparation of Olefins.—The procedure was adapted from that reported by Edgar, Calingaert and Marker.[14]

2,3-Dimethyl-2-pentene, b.p. 93–94° (744 mm.), lit.[15a] b.p. 94° (760 mm.): Gas chromatography through a 12′ column containing 30% tricresyl phosphate on firebrick at 82° and a helium flow rate of 95 ml./min. indicated the presence of 83% alkene.

2,3-Dimethyl-2-hexene, b.p. 117–119° (743 mm.), lit.[15b] 119° (760 mm.): Gas chromatographic analysis showed a peak corresponding to 89% olefin.

1,2-Dimethylcyclopentene, b.p. 103–105° (741 mm.), lit.[15c] 103–105° (760 mm.). Vapor phase chromatographic analysis disclosed a peak corresponding to 91% cycloalkene.

1,2-Dimethylcyclohexene, b.p. 135–137° (747 mm.), lit.[15d] 136° (760 mm.). Gas chromatography indicated the presence of 70% homogeneous cycloölefin.

2,2,3,3-Tetramethylaziridine. (A) **Chloronitrosation.**—The following general procedure for the addition of nitrosyl chloride to the fully substituted olefins appeared to be most suitable. To a well-stirred solution of 0.1 mole of 2,3-dimethyl-2-butene in 200 ml. of absolute methanol cooled in a Dry Ice–acetone-bath was added the theoretical amount of nitrosyl chloride gas (The Matheson Co., Inc., Rutherford, N.J.). During the course of addition, the reaction mixture became intensely blue and the nitroso chloride analog partially separated from solution. On completion of the addition of gaseous nitrosyl chloride, the cooling bath was removed and the mixture was rapidly stirred for 0.5 hour. The blue solution was slowly poured into a liter of ice-water and the nitroso compound separated as a blue solid in quantitative yield. The sublimed blue compound melted at 122–123°, lit.[16] 122°, with the evolution of gas.

(B) **Reduction.**—After an extensive study of the reduction of 2,3-dimethyl-2-chloro-3-nitrosobutane (V, R = CH_3) with a spectrum of reducing agents which included $LiAlH_4$, $NaBH_4$, Al(Hg), Zn–acetic acid, Zn–HCl and $SnCl_2$–HCl, the following synthetic procedure employing the latter reagent proved successful. A solution of 90 g. (0.4 mole) of stannous chloride dihydrate (reagent grade, Fisher Certified, ACS) in 120 ml. of concentrated HCl (sp. gr. 1.19, 37–38%) in a 500-ml. reaction flask was cooled in an ice-bath to 5°. At this point, the bath was removed and a tenth mole of the nitroso chloride was added in *one* portion (addition in small amounts gives lower yields of product) with vigorous stirring. The reaction temperature climbed to approximately 55° in the course of an hour, accompanied by the gradual disappearance of the blue nitroso chloride (experiments effected

(10) (a) It is noted for comparison that the reduction of tetramethylethylene nitroso chloride (V, R = CH_3) with HBr and red phosphorus in glacial acetic acid at 12° afforded a basic product which on treatment with base gave α,α,β-trimethylallylhydroxylamine *via* the proposed reaction sequence[9e]

$$Me_2CCl \underset{Me_2CNO}{\overset{HBr(P)}{\longrightarrow}} Me_2CCl \underset{Me_2CNHOH}{\overset{OH^-}{\longrightarrow}} MeC{=}CH_2 \quad (Me_2CNHOH)$$

(b) Consideration had been given to the possibility that ring closure may have occurred during reduction; however, it seems very unlikely that under such strongly acidic conditions the protonated amino group could participate in a cyclization process by either displacing the chloride atom or attacking an incipient carbonium ion.

(11) The protonated imine (I, R = CH_3) appears to be extremely resistant to attack to thiourea which cleaves the fully substituted imine 10^{-6} times the rate observed for the ring opening reaction of the parent aziridinium ion (unpublished results). In concurrence with this observation is the remarkable stability of 2,2-diphenyl-3,3-dimethylethylenimine to hydrolysis by aqueous sulfuric acid.[7]

(12) In harmony with this observation, Fanta has reported that cyclohexenimine showed an N–H stretching vibration at 3.1 μ also; O. E. Paris and P. E. Fanta, THIS JOURNAL, **74**, 3007 (1952).

(13) Melting and boiling points are uncorrected. Infrared spectra were measured with a Perkin–Elmer model 21 spectrophotometer with sodium chloride optics using neat liquids. Gas chromatography was effected with a Fisher–Gulf partitioner, model 300, equipped with an automatic integrater system. The n.m.r. spectra were run at room temperature employing a Varian high resolution spectrometer (model V-4300B with super stabilizer operating at 40 megacycles). Measurements of peak positions are relative to the external benzene reference. Microanalyses were performed by William Saschek, University of Chicago.

A sample of 2,3-dimethyl-2-butene was the gift of the Humble Oil and Refining Co., Baytown, Tex.

(14) G. E. Edgar, G. Calingaert and R. E. Marker, THIS JOURNAL, **51**, 1483 (1929).

(15) (a) G. Egloff, "Physical Constants of Hydrocarbons," Reinhold Publishing Corp., New York, N. Y., 1939, Vol. I, p. 209; (b) Vol. I, p. 226; (c) Vol. II, p. 308; (d) Vol. II, p. 330.

(16) J. Thiele, *Ber.*, **27**, 454 (1894).

at controlled temperatures, *viz.*, 5, 15 and 25°, produced poorer and variable yields of chloroamine). The clear, colorless solution was allowed to cool gradually to room temperature.

Cyclization.—The reaction mixture from the reduction was added dropwise to a rapidly stirred, ice-cooled solution of 2 moles of sodium hyroxide in a liter of water. The alkaline mixture was distilled into an ice-cooled receiver until a freshly collected portion of the distillate was found to be neutral. The distillate was made strongly basic with potassium hydroxide and extracted twice with ether. Fractionation (over sodium metal) afforded a 79% yield of 2,2,3,3-tetramethylaziridine (I, R = Me), b.p. 104–104.5° (744 mm.), $n^{20}D$ 1.4220. Gas chromatography through a 6' column containing 30% triethylene glycol on acid-washed firebrick (50–60 mesh) at 100° and a helium flow rate of 100 ml./min. revealed a peak corresponding to >98% tetramethylaziridine with a retention time of 23.0 minutes. The infrared spectrum of the neat liquid in a 25 μ cell was characterized by several prominent absorptions at 3200, 2910, 1465, 1380, 1175, 1065 and 830 cm.$^{-1}$. The n.m.r. spectrum showed a single, sharp peak at 217 c.p.s. (relative to external benzene at 40 megacycles).

Anal. Calcd. for $C_6H_{13}N$: C, 72.66; H, 13.21; N, 14.12. Found: C, 72.96; H, 13.47; N, 13.75.

2,2,3-Trimethyl-3-ethylaziridine.—In precisely the same manner, 0.1 mole of 2,3-dimethyl-2-pentene was quantitatively converted to the nitroso chloride. The blue product was not characterized but directly reduced with stannous chloride. Ring closure of the resulting chloroamine was accomplished with 4 equivalents of aqueous sodium hydroxide. Fractional distillation over sodium metal gave a 71% yield of the desired aziridine analog, b.p. 129–129.5° (751 mm.), $n^{20}D$ 1.4312. Vapor phase chromatographic analysis (triethylene glycol column 102°) disclosed a peak corresponding to >98% imine with a retention time of 26.6 minutes. The infrared spectrum disclosed prominent absorption bands at 3200, 2920, 1465, 1385, 1165 and 830 cm.$^{-1}$. The infrared and n.m.r. spectra were in accord with the assigned structure.

Anal. Calcd. for $C_7H_{15}N$: C, 74.27; H, 13.35; N, 12.37. Found: C, 74.47; H, 13.34; N, 12.00.

2,2,3-Trimethyl-3-propylaziridine.—The conversion of 0.1 mole of 2,3-dimethyl-2-hexene to the nitroso chloride proceeded smoothly at −70° in quantitative yield. The nitroso compound (probably a mixture of isomers) was processed successively with stannous chloride–HCl and then an excess of aqueous alkali. Careful distillation of the basic product afforded an 84% yield of the desired ethylenimine derivative, b.p. 150–150.5° (747 mm.), $n^{20}D$ 1.4339. Gas chromatography at 102.5° indicated the imine was >98% pure and possessed a retention time of 44.0 minutes. The infrared spectrum was characterized by several prominent absorption frequencies at 3200, 2920, 1465, 1380, 1260, 1165, 1080, 1050 and 835 cm.$^{-1}$. The n.m.r. spectrum appeared to be consistent with expectations.

Anal. Calcd. for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.64; H, 13.67; N, 10.62.

1,2,-Dimethylcyclopentenimine.—Treatment of 0.1 mole of 1,2-dimethylcyclopentene with gaseous nitrosyl chloride in a Dry Ice–acetone-bath afforded the desired 1,2-dimethyl-1-chloro-2-nitroso cyclopentane in excellent yield. After careful reduction with $SnCl_2$–concd. HCl, the resulting chloroamine was basified with an excess of sodium hydroxide solution to induce cyclization to the bicyclic imine. Fractional distillation of the basic material through a 24'' tantalum spiral column produced a 73% yield of the ethylenimine analog, b.p. 134–135°, $n^{20}D$ 1.4550. Gas chromatographic analysis revealed that the imine was 93% pure and had a retention time of 30.5 minutes at 108°. The n.m.r. spectrum of this compound revealed resonance lines at 214 c.p.s. (methyl protons) and 198 c.p.s. (ring hydrogens). The infrared spectrum showed prominent absorptions at 3225, 2920, 1445, 1410, 1385, 1292, 1262, 1220, 1050, 990, 865, 780 and 685 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{13}N$: C, 75.61; H, 11.78; N, 12.60. Found: C, 75.31; H, 11.76; N, 12.68.

1,2-Dimethylcyclohexenimine.—The chloronitrosation of 0.1 mole of 1,2-dimethylcyclohexene at −70° produced in excellent yield the desired 1,2-dimethyl-1-chloro-2-nitrosocyclohexane which on crystallization from absolute ethanol gave a melting point of 78–79°.

Anal. Calcd. for $C_8H_{14}NOCl$: Cl, 20.19. Found: Cl, 20.29.

The bicyclic imine was obtained by successive treatment of the nitroso chloride with stannous chloride–concd. HCl reagent and four equivalents of aqueous sodium hydroxide solution. Purification afforded a 76% yield of the fully substituted imine, b.p. 165–165.5° (750 mm.), $n^{20}D$ 1.4665. Vapor phase chromatographic analysis at 105° disclosed that the imine was homogenous (>98% pure) and had a retention time of 62.0 minutes. The n.m.r. spectrum disclosed resonance lines at 217 (methyl protons), 210 and 201 c.p.s. (ring hydrogens). The infrared spectrum showed prominent absorption bands at 3225, 1445, 1385, 1360, 1292, 1250, 1190, 1145, 1087, 1035, 1015, 985, 970, 905, 865, 825 and 805 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{15}N$: C, 76.73; H, 12.07; N, 11.18. Found: C, 76.52; H, 11.87; N, 10.95.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF BOSTON UNIVERSITY, BOSTON 15, MASS.]

Compounds Related to Podophyllotoxin. XI. An Unusual Stobbe Condensation[1]

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Stobbe condensation of methyl 2-(3',4',5'-trimethoxybenzoyl)-4,5-methylenedioxybenzoate with dimethyl succinate gives a product which was previously regarded as methyl 1-(3',4',5'-trimethoxyphenyl)-4-hydroxy-6,7-methylenedioxy-2-naphthoate but which is now shown to be methyl 1-hydroxy-4-(3',4',5'-trimethoxyphenyl)-6,7-methylenedioxy-2-naphthoate. The revision of structure follows from the infrared absorption of the condensation product, its reluctance to methylate with diazomethane, its mode of synthesis, and its non-identity with the authentic 4-hydroxy-2-naphthoate isomer. The tetralone, methyl 1-(3',4',5'-trimethoxyphenyl)-4-oxo-6,7-methylenedioxy-1,2,3,4-tetrahydro-2-naphthoate, on dehydrogenation with sulfur gives the authentic 4-hydroxy-2-naphthoate isomer. Acetylation yields the corresponding 4-acetoxy-2-naphthoate. The tetralone starting material with isopropenyl acetate plus a trace of acid forms the enol acetate, which with sulfur aromatizes to the same 4-acetoxy-2-naphthoate. A reaction path by which the Stobbe condensation can give rise to the 1-hydroxy-2-naphthoate isomer is suggested.

Cyclization of benzhydrylsuccinic acid I gave a keto acid, for which several structures could be written.[2] To show that structure II for the cyclized keto acid was correct, its methyl ester III was aromatized to the corresponding 4-hydroxy-2-naphthoic methyl ester V. This hydroxy ester V was expected to be identical with the same compound reported before as the product from a Stobbe condensation.[3] However, the two ma-

(1) This investigation was supported by Research Grant CY-2891 from the National Cancer Institute, Public Health Service.

(2) W. J. Gensler, C. M. Samour, Shih Yi Wang and F. Johnson, THIS JOURNAL, **82**, 1714 (1960).

(3) W. Reeve and H. Myers, *ibid.*, **75**, 4957 (1953).