(18), 262 (71), 190 (45), 105 (100). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.41; H, 6.54. Found: C, 61.17; H, 6.51.

Isoxazolidine 11 (0.270 g, 15%): recrystallized from hexane, mp 67.5–69.0 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.11–7.26 (5 H, m), 4.34–4.16 (2 H, m), 3.99 (1 H, dd, J = 12 and 7 Hz), 3.72 (3 H, s), 3.38 (1 H, dd, J = 13 and 7 Hz), 2.81 (1 H, m), 1.84 (3 H, s), 1.30 (3 H, t); IR (KBr) 3070, 2980, 2950, 2900, 1745, 1680, 1600, 1580, 1440 cm^{-1}; mass spectrum (CI), m/z (relative intensity) 294 (14, M^+ + 1), 262 (89), 190 (100), 105 (88). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.41; H, 6.54. Found: C, 31.03; H, 6.31.

Acknowledgment. This research was supported by grants from the Petroleum Research Fund (13176-G1), the Pennsylvania State University Applied Research Laboratory/Naval Sea Systems Command to P.R.D., and the NSF (Grant CHE8100132) to S.M.W. We also acknowledge valuable discussions with Ms. T. Dunne and Drs. C. DeBrosse and L. M. Jackman. Partial support for the purchase of a Bruker WP-200 NMR instrument from the National Science Foundation is also gratefully acknowledged. We thank the American Hoechst Corp. for a generous gift of ethyl glyoxylate and Dr. Klaus Müller for a copy of ref 13c.

Registry No. 1, 7372-59-0; 2, 83077-18-3; 3, 83077-19-4; (*E*)-4, 81206-60-2; (*Z*)-4, 81206-61-3; 5, 83095-76-5; 6, 1137-96-8; 7, 19744-05-9; (*E*)-8, 83148-36-1; (*Z*)-8, 65628-23-1; 9, 769-60-8; 10, 83077-20-7; 11, 83077-21-8; 12, 83077-22-9; methacrolein, 78-85-3; phenylbromide, 108-86-1; 2-methyl-1-phenyl-2-propenol, 4383-08-8; vinyl acetate, 108-05-4; ethyl vinyl ether, 109-92-2; *N*-methylhydroxylamine hydrochloride, 4229-44-1; ethyl glyoxylate, 924-44-7.

Supplementary Material Available: The NOE difference spectra (stack plots) of compounds 2, 3, 5, 7, and 10–12 (7 pages). Ordering information is given on any current masthead page.

Stereoselective Indolizidine Synthesis: Preparation of Stereoisomers of Gephyrotoxin-223AB

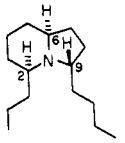
David J. Hart* and Yeun-Min Tsai

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

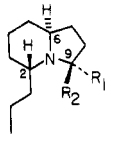
Received April 20, 1982

Indolizidines 2 and 3 were prepared and shown to be stereoisomers of the Dendrobatid alkaloid gephyrotoxin-223AB. A potentially useful entry to the 5-hexenyl radical manifold and an unusual ester to ketone transformation are described.

Over 90 alkaloids, several of which possess interesting pharmacological properties, have been detected in extracts from the skins of frogs belonging to the genus *Dendrobates*.[1,2] The structures of several of these alkaloids have been determined. A lack of sufficient quantities of pure substances, however, has obstructed structure determination of most of these alkaloids. On the basis of a gas chromatography–mass spectrometry survey, Daly and his co-workers suggested 2,9-disubstituted 1-azabicyclo-[4.3.0]nonane structures for several Dendrobatid alkaloids.[1] As part of a cooperative effort that led to the suggestion that gephyrotoxin-223AB (GTX-223AB) has structure 1,[3] we prepared the GTX-223AB stereoisomers 2 and 3. This report presents the details of our syntheses and discusses chemical and spectral data that support the stereochemical assignments.[4]



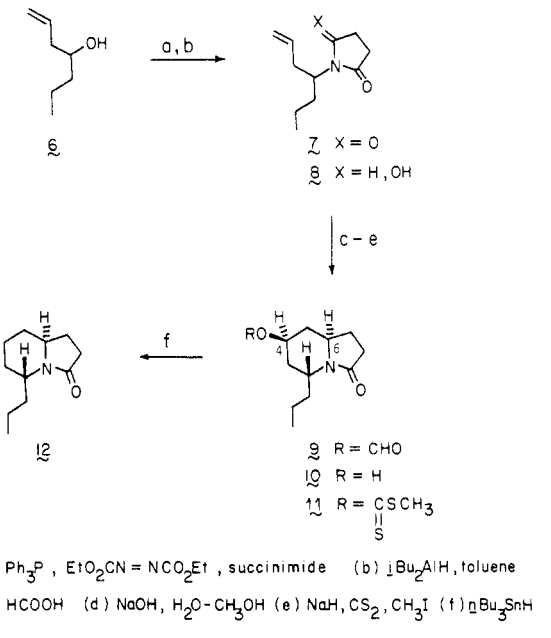
1



2 R_1 = H, R_2 = n-C_4H_9

3 R_1 = n-C_4H_9, R_2 = H

Scheme I



Our approach to the synthesis of 2 and 3 was based on the discovery that formic acid induced cyclizations[5] of

(1) Daly, J. W.; Brown, G. B.; Mensah-Dwumah, M.; Myers, C. W. *Toxicon* **1978**, *16*, 163.

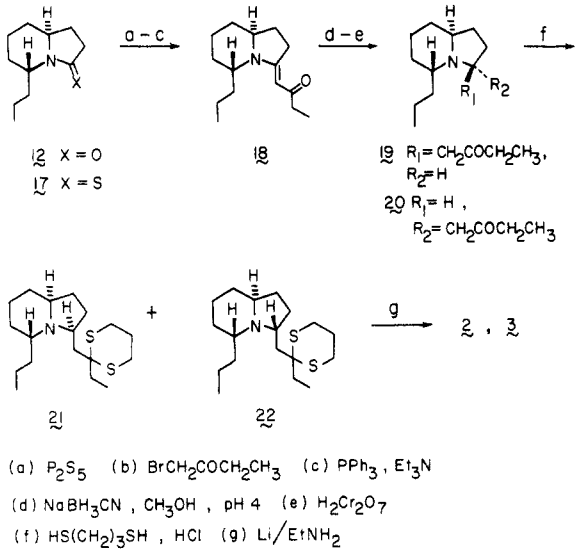
(2) Daly, J. W.; Mensah-Dwumah, M. *Toxicon* **1978**, *16*, 189. Daly, J. W.; Tokuyama, T.; Fujiwara, T.; Highet, R. J.; Karle, I. L. *J. Am. Chem. Soc.* **1980**, *102*, 830.

(3) Spande, Th. F.; Daly, J. W.; Hart, D. J.; Tsai, Y.-M.; Macdonald, T. L. *Experientia* **1981**, *37*, 1242.

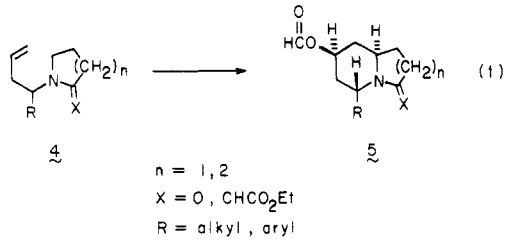
(4) For other studies directed toward GTX-223AB, see: Macdonald, T. L. *J. Org. Chem.* **1980**, 45, 193. Stevens, R. V.; Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1982**, 103. For related work, see Sonnet, P. E.; Netzel, D. A.; Mendoza, R. *J. Heterocycl. Chem.* **1979**, *16*, 1041 and references cited therein.

0022-3263/82/1947-4403$01.25/0

Scheme II

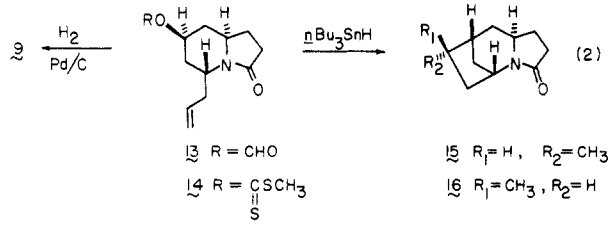


carbinolamides of type **4** give indolizidines and quinolizidines of type **5** *with high stereoselectivity* (eq 1).[6,7] The

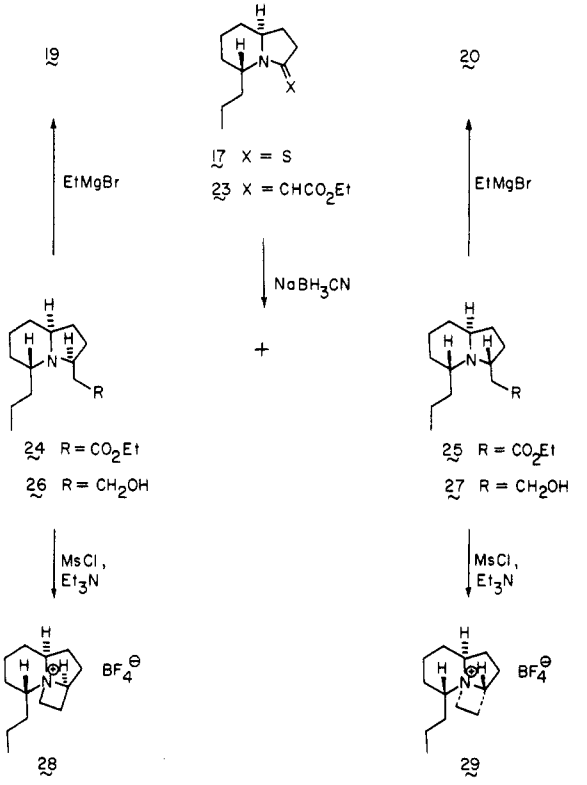


(1)

cyclization required for the preparation of **2** and **3** was examined as outlined in Scheme I. Thus, treatment of *n*-butyraldehyde with allylmagnesium bromide gave homoallylic alcohol **6** (85%), which was converted to imide **7** (67%) as previously described.[7] Imide **7** was reduced with diisobutylaluminum hydride and the resulting crude carbinolamide **8** (96%) was treated with formic acid to give formate **9** (65%) along with trace amounts of other bicyclic lactams.[8] The stereochemical assignment for **9** was based on spectral and chemical data. The infrared spectrum of **9** exhibited a normal lactam carbonyl at 1695 cm^{-1}. This data requires that H_6 occupy an axial site on the rigid indolizidinone framework.[9] In addition, H_4 appears as a triplet of triplets (J = 10, 4 Hz), establishing that it is also axially disposed.[10] The axial disposition of the C(2) propyl group was established by the transformations shown in eq 2. Catalytic hydrogenation of lactam **13**, prepared in a



Scheme III

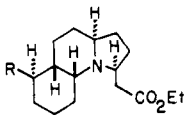


straightforward manner from diallylcarbinol,[11] afforded lactam **9** (100%). Lactam **13** was converted to xanthate **14** (82%), which was treated with tri-*n*-butyltin hydride to afford a 2:1 mixture of tricyclic lactams **15** and **16** (74%).[12-14] This result clearly establishes the axial disposition of the C(2) side chain in **13** and **9**. With the relative stereochemistry at C(2) and C(6) of **9** established, the undesired oxygen functionality at C(4) was removed by use of the Barton procedure (71% from **9** to **12**).[12]

The syntheses of **2** and **3** were completed as outlined in Scheme II. Lactam **12** was treated with phosphorus pentasulfide to afford thiolactam **17** (82%). Sequential treatment of **17** with 1-bromo-2-butanone,[15] triethylamine, and triphenylphosphine gave vinylogous amide **18** (92%).[16] Reduction of **18** with either sodium cyanoborohydride[17] or Pt-H_2-AcOH[18] followed by an oxidative workup (Jones reagent)[19] gave a mixture of isomeric amino ketones **19** and **20** (70–75%). Difficulties were encountered during attempts to separate **19** and **20** due to the ease with which they interconverted upon chromatography over silica gel or alumina, presumably via a retro-Michael–Michael

(5) For a recent review, see: Speckamp, W. N. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 345.
(6) Hart, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 397.
(7) Hart, D. J. *J. Org. Chem.* **1981**, *46*, 367.
(8) For a study which reveals the mechanistic details of this reaction, see: Hart, D. J.; Tsai, Y.-M. *Tetrahedron Lett.* **1981**, 1567.
(9) Indolizidinones of type **9** cannot adopt a conformation in which the C(6)–C(7) bond is axially disposed on a chair piperidine without destroying amide resonance.
(10) For an appropriate discussion, see: Emsley, J. W.; Feeney, J.; Sutcliffe, L. H. "High Resolution Nuclear Magnetic Resonance Spectroscopy"; Pergamon Press: New York, 1966; Vol. 2, pp 696–710.
(11) Lactam **13** was prepared from diallylcarbinol via a sequence identical with that used to transform **6** into **9**. The details will be presented in the Ph.D. thesis of Y.-M. Tsai, Ohio State University, Columbus, OH.
(12) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
(13) This represents an obviously simple but heretofore unused entry to the 5-hexenyl radical manifold. We do not know whether **15** or **16** is the major stereoisomer.
(14) For a recent review of radical cyclizations, see: Beckwith, A. L. J.; Ingold, K. U. In "Rearrangements in Ground and Excited States"; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, pp 182–219.
(15) Catch, J. R.; Elliott, D. F.; Hey, D. H.; Jones, E. R. H. *J. Chem. Soc.* **1948**, 272.
(16) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710.
(17) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.
(18) Wenkert, E.; Reynolds, G. D. *Aust. J. Chem.* **1969**, *22*, 1325.
(19) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39.

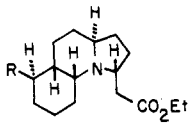
Table I. Chemical Shifts of Selected β-Amino Esters[a]



30

a R=H

b R=$CH_2CH_2OSiPh_2$



31

a R=H

b R=$CH_2CH_2OSiPh_2$

compd	H_2	H_6	H_9	H_α[b]	H_α[b]
24	2.97	2.38	3.21	2.59	2.24
30a	2.90	2.37	3.14	2.61	2.18
30b	3.07	2.42	3.22	2.60	2.22
25	2.59	3.08	3.44	2.53	2.24
31a	2.60	3.10	3.43	2.52	2.23
31b	2.81	3.14	3.42	2.49	2.28

[a] All spectra were taken in C_6D_6. Data are reported in parts per million downfield from internal tetramethylsilane. [b] H_α refers to the diastereotopic hydrogens of the CH_2CO_2Et group.

process. Thus we assumed that the major product was the thermodynamically most stable indolizidine and assigned it structure **19**.[20] Supporting evidence for this assignment will be presented later (vide infra). When a mixture of crude **19** and **20** was treated with propane-1,3-dithiol and hydrochloric acid, thioketals **21** and **22** (60% and 23%, respectively, from **18**) were obtained and separated by column chromatogrphy. Reduction of **21** and **22** with lithium in ethylamine[21] gave **2** (60%) and **3** (26%), respectively. Indolizidines **2** and **3** were identical with samples prepared by Spande and isomeric with authentic[3] and synthetic[3,22] GTX-223AB.[23]

In an attempt to obtain better evidence for the stereochemical assignments made on thermodynamic grounds above, we performed the experiments shown in Scheme III. Thus, treatment of thiolactam **17** with ethyl bromoacetate followed by triethylamine and triphenylphosphine gave vinylogous urethane **23** (99%).[16] The same transformation was accomplished by treating **17** sequentially with methyl iodide and the dibasic magnesium salt of ethyl hydrogen malonate (82%).[24] Treatment of **23** with sodium cyanoborohydride[17] gave a mixture of amino esters **24** (50%) and **25** (27%). Unlike amino ketones **19** and **20**, esters **24** and **25** were configurationally stable and easily separated by column chromatography. The stereochemical assignments of **24** and **25** were based in part on a comparison of their ^1H NMR spectra with those of intermediates prepared during the course of our synthesis of the Dendrobatid alkaloid gephyrotoxin.[25] For example, the chemical shifts of H_2, H_6, and H_9 and the multiplicities of H_6 and H_9 in **24** and **25** compare favorably with those recorded for **30a,b** and **31a,b**, respectively (see Table I). In addition, on the basis of the stereochemical course of the sodium cyanoborohydride reductions performed during the gephyrotoxin synthesis, it is reasonable that amino ester **24** be the major reduction product.

We initially tried to correlate the structures of **24** and **25** with those of **2** and **3** as outlined in Scheme III. Reduction of **24** and **25** with lithium aluminum hydride gave amino alcohols **26** (97%) and **27** (96%). Once again, the ^1H NMR spectra of these alcohols were similar to related intermediates in the gephyrotoxin series. We intended to convert **26** and **27** to derivatives suitable for coupling with lithium diethylcuprate. Treatment of **26** and **27** with either tosyl chloride or mesyl chloride at 0 °C, however, afforded quaternary ammonium salts **28** (61%) and **29** (86%), isolated as their tetrafluoroborate salts. Although cyclizations of γ-amino alcohol derivatives to azetidines and azetidinium ions are known,[26] the ease with which **26** and **27** can be converted to salts **28** and **29** is noteworthy.

The correlation of **24** and **25** with **2** and **3** was finally accomplished in the following manner. Independent treatment of **24** and **25** with ethylmagnesium bromide (5.0 equiv, 7 h, 25 °C) followed by addition of the reaction mixture to water gave **19** (65%) and **20** (69%), respectively, establishing the stereochemical relationship between the two C(9) side-chain series. This ester to ketone conversion is also noteworthy. We initially felt that amino esters **24** and **25** might react with Grignard reagents to give nitrogen chelated tetrahedral intermediates that would break down slowly, thus facilitating the desired ester to ketone transformation.[27] The observation that a large excess of ethylmagnesium bromide and long reaction times were necessary, however, led us to consider a mechanistic pathway other than direct carbonyl addition. Specifically, we thought that sequential enolization of **24** (**25**),[28] fragmentation to afford a ketene,[29] trapping of the ketene with the Grignard reagent,[30] and protonation upon aqueous workup might afford a less conventional pathway for the conversion of **24** (**25**) to **19** (**20**). Attempts to demonstrate the intermediacy of the ester enolate, however, met with failure. Thus, whatever the mechanism by which **24** (**25**) is converted to **19** (**20**), enolization of the starting β-amino ester does not appear to be involved.[31]

In summary, the synthesis of two GTX-223AB stereoisomers has been accomplished by a route that should be amenable to the synthesis of other indolizidine alkaloids. During the course of gathering chemical evidence for the stereochemical assignments, the Barton deoxygenation procedure was used to enter the hexenyl radical manifold. In addition, another example of what may be a chelation-controlled Grignard-mediated ester to ketone transformation was noted.

Experimental Section

All melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected as are boiling points. ^1H nuclear magnetic resonance spectra were recorded on Varian Associates EM-390, Varian Associates EM-360, or Bruker WP-200 spectrometers and are reported in parts per million from internal tetramethylsilane on the δ scale. Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet,

(20) Our expectation that **19** is thermodynamically more stable than **20** is based on reports that indolizidines show a large preference for conformations in which the nitrogen lone pair and angular hydrogen atom adopt an anti-periplanar relationship: Skvortsov, I. M. *Russ. Chem. Rev.* **1979**, *48*, 262 and references cited therein.

(21) Crossley, N. S.; Henbest, H. B. *J. Chem. Soc.*, **1960**, 4413.

(22) We thank Dr. John W. Daly and Dr. Thomas F. Spande for performing these comparisons at the National Institutes of Health.

(23) For a description of the comparisons see reference 3.

(24) Gugelchuk, M. M.; Hart, D. J.; Tsai, Y.-M. *J. Org. Chem.* **1981**, *46*, 3671.

(25) Hart, D. J. *J. Org. Chem.* **1981**, *46*, 3576.

(26) Capon, B.; McManus, S. P. "Neighboring Group Participation"; Plenum Press: New York, 1976; Vol. 2, pp 227–262. Galinovsky, F.; Nesvadba, H. *Monatsh. Chem.* **1954**, *85*, 1300.

(27) Mukaiyama, T.; Araki, M.; Takei, H. *J. Am. Chem. Soc.* **1973**, *95*, 4763.

(28) β-Amino ester enolates appear to be fairly stable to β eliminations: Clark, D. E.; Meredith, R. F. K.; Ritchie, A. C.; Walker, T. *J. Chem. Soc.* **1962**, 2490. Still, W. C.; Schneider, M. J. *J. Am. Chem. Soc.* **1977**, *99*, 948. Helquist, P.; Yu, L. *Tetrahedron Lett.* **1978**, 3423.

(29) Sullivan, D. F.; Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 2038.

(30) Tidwell, T. T. *Tetrahedron Lett.* **1979**, 4615.

(31) For other ester to ketone transformations, see: Majetich, G.; Grieco, P. A.; Bongers, S.; Erman, M. G.; Langs, D. A. *J. Org. Chem.* **1981**, *46*, 209 and references cited therein.

q = quartet, qu = quintet, se = septet, m = multiplet), coupling constants in hertz, integration, interpretation]. ^{13}C nuclear magnetic resonance spectra were recorded on a Bruker WP-80 spectrometer and are reported in parts per million from internal tetramethylsilane. Infrared spectra were taken with a Perkin-Elmer 457 instrument. Mass spectra were recorded on an AEI-MS9 instrument at an ionization energy of 70 eV. Samples on which exact masses were measured exhibited no significant peaks at m/e greater than those of the parent. Combustion analyses were performed by Micro-Analysis, Inc., Wilmington, DE.

Solvents and reagents were dried and purified prior to use when deemed necessary: tetrahydrofuran, diethyl ether (distilled from Na metal); toluene (distilled from calcium hydride); methanol (distilled from magnesium methoxide); chloroform (passed through activity I alumina). All reaction temperatures refer to those of the reaction mixture. Reactions requiring an inert atmosphere were run under a blanket of nitrogen or argon. Formic acid (97%) was used in all cyclizations. Analytical thin-layer chromatography was performed with EM Laboratories 0.25 mm thick precoated silica gel 60 F-254 plates. Column chromatography was performed over EM Laboratories silica gel (70–230 mesh) and Woelm neutral alumina. GLC analysis was done on a Varian Aerograph Series 1400 instrument equipped with a thermal conductivity detector.

The synthesis of imide **7** has been described elsewhere.[7]

1-(1-Hepten-4-yl)-5-hydroxy-2-pyrrolidinone (8). To a solution of 28.3 g (0.145 mol) of imide **7** in 360 mL of toluene at −60 °C was added 360 mL of diisobutylaluminum hydride (25 wt %) in toluene at a rate that kept the temperature between −60 and −65 °C. The progress of the reaction was monitored by TLC analysis of aliquots taken directly from the reaction mixture (silica gel; ethyl acetate–hexane, 3:1). The cold mixture was stirred for an additional 30 min and poured into 500 mL of cold 5% aqueous sulfuric acid. The resulting mixture was extracted with two 500-mL portions of dichloromethane. The extracts were dried (Na_2SO_4) and concentrated in vacuo to give 27.4 g (96%) of crude hydroxy lactam **8** as a pale-yellow liquid, which was used directly in the preparation of formate **9**. A portion of this crude product (507 mg) was chromatographed over 25 g of silica gel (eluted with ethyl acetate–hexane, 3:4, followed by ethyl acetate–hexane, 3:1) to give 300 mg of pure **8** as a yellow oil: IR ($CHCl_3$) 3590 (weak), 3490 (br), 1680 cm^{-1}; NMR ($CDCl_3$) δ 0.55–3.18 (m, 13 H), 3.55–4.35 (m, 1 H, OH), 4.35–6.35 (m, 5 H, NCH, OCH, vinylic H); mass spectrum, m/e (relative intensity) 179 (9), 156 (100), 154 (21), 138 (91), 136 (7), 110 (46), 108 (10), 100 (23), 84 (21), 83 (19).

***rel*-(2*R*,4*R*,6*R*)-9-Oxo-2-propyl-1-azabicyclo[4.3.0]nonan-4-yl Formate (9).** To a stirred solution of 250 mL of formic acid cooled in an ice bath was added dropwise 27.4 g (0.13 mol) of carbinolamide **8** via pipet. The resulting straw-colored solution was stirred at room temperature for 45 min, and the formic acid was removed in vacuo with slight warming. The residual oil was stirred with 320 mL of saturated sodium bicarbonate solution for 15 min and extracted with two 400-mL portions of dichloromethane. The extracts were dried (Na_2SO_4) and concentrated in vacuo to give 27.4 g of a brown oil. This oil was chromatographed over 500 g of silica gel (eluted with ethyl acetate–hexane, 3:4, followed by ethyl acetate) to afford 20.3 g (65%) of formate **9** as a pale-yellow oil: IR (CCl_4) 1730, 1695 cm^{-1}; NMR ($CDCl_3$) δ 0.77–2.60 (m, 15 H), 3.43–4.00 (m, 1 H, NCH), 4.10–4.57 (m, 1 H, NCH), 5.1 (tt, J = 10, 4 Hz, 1 H, COOCH), 7.97 (s, 1 H, HCOO); mass spectrum, m/e (relative intensity) 225 (8), 182 (11), 136 (100), 110 (3), 108 (10), 84 (9); exact mass calcd for $C_{12}H_{19}NO_3$ m/e 225.1365, found m/e 225.1369.

***rel*-(2*R*,4*R*,6*R*)-4-Hydroxy-2-propyl-1-azabicyclo[4.3.0]nonan-9-one (10).** To a solution of 20.3 g (90.0 mmol) of formate **9** in 120 mL of methanol was added a solution of 4.9 g (122 mmol) of sodium hydroxide in 23 mL of water. The resulting solution was stirred at room temperature for 50 min and partitioned between 500 mL of dichloromethane and 200 mL of water. The aqueous phase was extracted with two 200-mL portions of dichloromethane and the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to give 17.2 g (97.3%) of crude carbinol lactam **10** as a pale-yellow oil. This material was used directly for the preparation of xanthate **11**. A portion of the crude lactam was chromatographed over silica gel (eluted with ethyl acetate–hexane, 19:1) to afford a sample of pure **10**: IR (neat) 3380 (br), 1660 cm^{-1}; NMR ($CDCl_3$) δ 0.70–2.57 (m, 15 H), 2.57–3.27 (br s, 1 H, OH), 3.37–4.47 (m, 3 H, NCH, OCH); exact mass calcd for $C_{11}H_{19}NO_2$ m/e 197.1415, found m/e 197.1418.

***rel*-(2*R*,4*R*,6*R*)-9-Oxo-2-propyl-1-azabicyclo[4.3.0]nonan-4-yl *S*-Methyl Dithiocarbonate (11).** A mixture of 3.69 g (0.154 mol) of sodium hydride, 17.2 g (0.087 mol) of carbinol lactam **10**, 0.154 g of imidazole, and 380 mL of dry tetrahydrofuran was heated to reflux under nitrogen for 2.5 h followed by the addition of 23.0 mL (0.370 mol) of carbon disulfide. The solution was warmed under reflux for 30 min and 23.0 mL (0.37 mol) of methyl iodide was added. The mixture was warmed for another 60 min and the reaction mixture was partitioned between 700 mL of dichloromethane and 700 mL of water. The aqueous phase was extracted with 200 mL of dichloromethane, and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give 27.5 g of a dark-brown oil. The oil was chromatographed over 500 g of silica gel (eluted with ethyl acetate) to give 22.4 (89.3%) of xanthate **11** as a viscous yellow oil: IR ($CHCl_3$) 1670, 1060 cm^{-1}; NMR (CCl_4) δ 0.75–2.42 (m, 15 H), 2.52 (s, 3 H, SCH_3), 3.38–4.02 (br s, 1 H, NCH), 4.02–4.55 (m, 1 H, NCH), 5.75 (tt, J = 11, 4 Hz, 1 H, OCH); mass spectrum, m/e (relative intensity) 287 (1), 254 (4), 240 (4), 180 (100), 179 (6), 136 (48), 179 (16), 117 (16), 108 (8), 97 (4), 84 (76); exact mass calcd for $C_{13}H_{21}NO_2S_2$ m/e 287.1014, found m/e 287.1018.

Anal. Calcd for $C_{13}H_{21}NO_2S_2$: C, 54.32; H, 7.37. Found: C, 55.10; H, 7.44.

***rel*-(2*R*,6*S*)-2-Propyl-1-azabicyclo[4.3.0]nonan-9-one (12).** To a solution of 27.2 g (93.4 mmol) of tri-*n*-butyltin hydride in 540 mL of dry toluene under reflux was added 18.0 g (62.7 mmol) mol) of xanthate **11** in 540 mL of dry toluene over a period of 2 h. The resulting solution was warmed under reflux for an additional 22 h, allowed to stand overnight at room temperature, and concentrated in vacuo. The residue was chromatographed over 500 g of silica gel (eluted with ethyl acetate) to afford 9.12 g (80%) of lactam **12** as a pale-yellow oil: IR (neat) 1690 cm^{-1}; NMR (CCl_4) δ 0.63–2.5 (m, 17 H), 3.17–3.77 (br s, 1 H, NCH), 3.83–4.33 (m, 1 H, NCH); ^{13}C NMR ($CDCl_3$) δ 13.64 (q), 18.60 (t), 19.27 (t), 25.00 (t), 27.19 (t), 29.95 (t), 31.99 (t), 33.55 (t), 47.58 (d), 52.92 (d), 173.37 (s); mass spectrum, m/e (relative intensity) 181 (3.6), 138 (100), 110 (1.4), 84 (2.6); exact mass calcd for $C_{11}H_{19}NO$ m/e 181.1466, found m/e 181.1470.

Catalytic Hydrogenation of Formate 13. A mixture of 10 mg of 5% palladium on charcoal, 61 mg (0.27 mmol) of formate **13**, and 2 mL of absolute ethanol was hydrogenated under an initial hydrogen pressure of 58.5 psi for 2 h. The resulting mixture was diluted with dichloromethane, dried with magnesium sulfate, and filtered through Celite. The filtrate was concentrated in vacuo to give 61 mg of a colorless oil, which was chromatographed over 5 g of silica gel (eluted with ethyl acetate) to give 61 mg 100% of a colorless oil that had identical NMR, IR, and TLC (ethyl acetate) characteristics as formate **9**.

***rel*-(1*R*,6*R*,8*R*,9*R*)-9-Methyl-3-oxo-2-azatricyclo[6.2.1.0^{2,6}]undecane (15) and *rel*-(1*R*,6*R*,8*R*,9*S*)-9-Methyl-3-oxo-2-azatricyclo[6.2.1.0^{2,6}]undecane (16).** To a solution of 304 mg (1.04 mmol) of tri-*n*-butyltin hydride in 6 mL of dry toluene heated to reflux under argon was added dropwise a solution of 192 mg (0.67 mmol) of xanthate **14** in 6 mL of dry toluene via a dropping funnel over a period of 50 min. The resulting solution was heated under reflux for another 17 h and the solvent was removed in vacuo to give 450 mg of a pale-yellow oil. This material was chromatographed over 20 g of silica gel (eluted with hexane–ethyl acetate, 3:7) to give 24.1 mg of a less polar material, which was distilled bulb to bulb to give 19 mg (16%) of a colorless oil identified as the reduction product: bp 60–70 °C (0.14 mmHg): IR (CH_2Cl_2) 1670 cm^{-1}; NMR (CCl_4) δ 0.90–2.38 (m, 12 H), 3.29–3.68 (m, 1 H, NCH), 4.08–4.40 (m, 1 H, NCH), 4.87–5.20 (m, 2 H, $=CH_2$), 5.54–6.05 (m, 1 H, CH=); continued elution gave 89 mg (74%) of a mixture of **15** and **16** as a colorless oil after bulb-to-bulb distillation [60–70 °C (0.14 mmHg)] separable by gas–liquid chromatography (6 ft × $^1/_8$ in. column packed with 10% OV-101 on Chrom W, Hp 80/100; column temperature, 185 °C; flow rate, 24 mL/min) in a ratio of 2:1. **15**: t_R = 7.4 min; IR (CH_2Cl_2) 1675 cm^{-1}; NMR ($CDCl_3$) δ 1.02 (d, J = 7 Hz, 3 H, CH_3), 1.28 (ddd, J = 14, 11, 6 Hz, 1 H), 1.34–1.44 (m, 2 H), 1.52 (dtd, J = 13, 11, 8 Hz, 1 H), 1.68 (dddd, J = 13, 6, 3, 2 Hz, 1 H), 1.78 (dtd, J = 13, 6, 2 Hz, 1 H), 1.91 (ddd, J = 14, 8, 3 Hz, 1 H),

2.00–2.21 (m, 3 H), 2.30–2.44 (m, 2 H), 3.66 (dddd, J = 14, 9, 8, 6 Hz, 1 H, NCH), 4.54 (br t, J = 4.5 Hz, 1 H, NCH); mass spectrum, m/e (relative intensity) 179 (20), 136 (100); exact mass calcd for $C_{11}H_{17}NO$ m/e 179.1310, found m/e 179.1315. **16**: t_R = 8.7 min; IR (CH_2Cl_2) 1670 cm^{-1}; NMR ($CDCl_3$) δ 1.12 (d, J = 7 Hz, 3 H, CH_3), 1.27 (ddd, J = 15, 11, 4 Hz, 1 H), 1.44–1.67 (m, 4 H), 1.94 (br d, J = 15 Hz, 1 H), 2.13–2.25 (m, 4 H), 2.30–2.40 (m, 2 H), 3.62–3.76 (m, 1 H, NCH), 4.47–4.55 (br s, 1 H, NCH); mass spectrum, m/e (relative intensity) 179 (20), 136 (100); exact mass calcd for $C_{11}H_{17}NO$: m/e 179.1310, found m/e 179.1314.

***rel*-(2*R*,6*S*)-2-Propyl-1-azabicyclo[4.3.0]nonane-9-thione (17).** A mixture of 3.71 g (16.6 mmol) of phosphorus pentasulfide, 100 mL of dry toluene, and 6.00 g (33.2 mmol) of lactam **12** was warmed to reflux under nitrogen for 30 min. The resulting solution phase was decanted, and the residual solid was crushed with a spatula followed by stirring with dichloromethane for 1 h. The resulting mixture was filtered, and the combined organic solutions were filtered again through Celite. The filtrate was concentrated in vacuo to give 6.00 g of an orange liquid which was bulb-to-bulb distilled to afford 4.80 g (73%) of thiolactam **17** as a light-yellow oil that solidified on standing: bp 110 °C (0.1 mm); mp 37–39 °C. The residue after the first filtration was stirred with 50 mL of water and 50 mL of dichloromethane and the aqueous phase was extracted with 50 mL of dichloromethane. The combined organic phases were dried (Na_2SO_4), concentrated in vacuo, and bulb-to-bulb distilled to give an additional 0.61 g (9%) of thiolactam **17** as a yellow solid: mp 36.5–38.5 °C; IR (neat) 1475, 1160, 1130 cm^{-1}; NMR ($CDCl_3$) δ 0.63–2.63 (m, 14 H), 2.63–3.20 (m, 2 H, C(S)CH_2), 3.53–4.16 (m, 1 H, NCH), 4.67–5.20 (br s, 1 H, NCH); mass spectrum, m/e (relative intensity) 197 (57), 196 (7), 168 (33), 164 (81), 155 (100), 154 (43), 122 (43); exact mass calcd for $C_{11}H_{19}NS$ m/e 197.1238, found m/e 197.1242.

Anal. Calcd for $C_{11}H_{19}NS$: C, 66.95; H, 9.70. Found: C, 66.99; H, 9.84.

1-[*rel*-(2*R*,4*S*)-2-Propyl-1-azabicyclo[4.3.0]nonan-9-ylidene]butan-2-one (18). To a solution of 2.61 g (13.2 mmol) of thiolactam **17** in 25 mL of dry ether was added 2.67 (17.7 mmol) of 1-bromo-2-butanone in 20 mL of dry ether, and the resulting solution was stirred under nitrogen at room temperature for 47 h. The ether layer was removed with a pipet and concentrated in vacuo to give a yellow oil (60.3 mg), which was dissolved in 65 mL of chloroform and returned to the original reaction vessel. The resulting solution was cooled in an ice bath followed by sequential addition of 3.46 g (13.2 mmol) of triphenylphosphine and 2.66 g (26.4 mmol) of triethylamine. The solution was stirred under nitrogen at room temperature for 2 h and concentrated in vacuo. The resulting solid residue was triturated with two 50-mL portions of ethyl acetate–hexane (1:9), and the combined extracts were concentrated in vacuo. The resulting yellow oil was treated with 30 mL of ethyl acetate–hexane (1:9) and filtered through Celite. The filtrate was concentrated in vacuo, and excess bromo ketone was removed under a pressure of 0.1 mm at room temperature to afford 3.96 g of a yellow oil. The oil was chromatographed over 150 g of silica gel (eluted with ethyl acetate–hexane, 3:7, followed by ethyl acetate–hexane, 1:1) to give 3.09 g (100%) of vinylogous amide **18** as a yellow oil. Part of this oil (2.74 g) was bulb-to-bulb distilled to give 2.54 g (92%) of **18** as a pale-yellow oil: IR ($CHCl_3$) 1625, 1530 cm^{-1}; NMR ($CDCl_3$) δ 0.82–2.48 (m with t, J = 5 Hz, at 1.10 and q, J = 5 Hz, at 2.31, 20 H, $COCH_2CH_3$, CH_3, CH_2), 2.93 (se, J = 6 Hz, 1 H, NCH), 3.27–3.93 (m, 3 H, allyl), 5.07 (s, 1 H, vinyl); mass spectrum, m/e (relative intensity) 235 (28), 206 (100), 192 (28), 188 (14), 178 (28), 164 (16), 136 (71); exact mass calcd for $C_{15}H_{25}NO$ m/e 235.1936, found m/e 235.1943.

1-[*rel*-(2*R*,6*S*,9*S*)-2-Propyl-1-azabicyclo[4.3.0]nonan-9-yl]butan-2-one (19). Method A. To a mixture of 399 mg of platinum oxide in a 500-mL Parr bottle were added 1.75 g (7.45 mmol) of vinylogous amide **18** and 50 mL of glacial acetic acid. The resulting mixture was hydrogenated under an initial hydrogen pressure of 60 psi for 160 min. Some magnesium sulfate was added, and the resulting mixture was filtered through Celite. The filtrate was concentrated in vacuo, and the residue was dissolved in 100 mL of dichloromethane. The solution was washed with 40 mL of saturated sodium bicarbonate solution and the aqueous phase was extracted with two 40-mL portions of dichloromethane. The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to give 1.64 g of a pale-yellow oil.

Part of this oil (1.55 g) was dissolved in 25 mL of acetone. To this solution cooled in an ice bath was added 1.42 mL of Jones reagent over a period of 10 min. The resulting green mixture was stirred with cooling for an additional 20 min followed by the addition of 2.5 mL of isopropyl alcohol. The mixture was stirred at 0 °C for another 5 min and solvent was removed in vacuo. The greenish residue was mixed with 50 mL of water and 5 g of sodium bicarbonate was added in small portions with stirring. The resulting mixture was extracted with 150 mL of dichloromethane. The organic layer was washed with two 50-mL portions of water, dried (Na_2SO_4), and concentrated in vacuo to give 1.45 g of a dark-orange oil. The oil was chromatographed over 260 g of silica gel [eluted with methanol (12% ammonia)–chloroform, 1.5:98.5] to give 747 mg (46%) of amino ketone **19** as a yellow oil [IR ($CHCl_3$) 1710 cm^{-1}; NMR ($CDCl_3$) 0.73–2.13 (m with t, J = 7 Hz, at 1.03, 20 H, CH_3, CH_2), 2.17–2.7 (m, 4.5 H), 2.73–3.33 (m, 2.5 H); NMR (C_6D_6) δ 0.70–1.87 (m with t, J = 7 Hz at 0.97, 20 H), 1.87–2.67 (m, 5 H, $C(O)CH_2$, NCH) 2.67–2.97 (m, 1 H, NCH), 2.97–3.33 (m, 1 H, NCH); ^{13}C NMR ($CDCl_3$) 7.77 (q), 14.38 (q), 19.18 (t), 20.88 (t), 23.48 (t), 27.85 (t), 28.76 (t), 29.80 (t), 32.41 (t), 37.08 (t), 46.67 (t), 53.04 (d), 54.44 (d), 56.01 (d), 210.14 (s); mass spectrum, m/e (relative intensity) 237 (5), 194 (100), 166 (46), 122 (70); exact mass calcd for $C_{15}H_{27}NO$, m/e 237.2092, found m/e 237.2096] and 238 mg (22%) of a mixture of **19** and **20** by NMR analysis and thin-layer chromatography (silica gel eluted with methanol (2% ammonia)–chloroform, 12:88; R_f 0.52 for **19** and R_f 0.35 for **20**).

Method B. To 33.8 mg (0.540 mmol) of sodium cyanoborohydride in 0.5 mL of dry methanol under nitrogen was added 122 mg (0.520 mmol) of vinylogous amide **18** in 0.5 mL of dry methanol followed by a trace of bromocresol green. To the resulting blue green solution was added dropwise a solution of 1.64 N hydrochloric acid in methanol until the solution maintained a yellow color. The resulting solution was stirred at room temperature for 30 min and poured into 3 mL of 1.5 N sodium hydroxide solution. The mixture was extracted with dichloromethane (2 × 15 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give 114 mg of a pale-green oil.

To the oil in 3 mL of acetone cooled in an ice bath was added 0.18 mL of Jones reagent over a period of 3 min. The reaction mixture was stirred at 0 °C for an additional 10 min and 10 drops of isopropyl alcohol was added. After the mixture was stirred at 0 °C for 5 min, the solvent was removed in vacuo and the greenish residue was mixed with 20 mL of water. Sodium bicarbonate was added in small portions with stirring until the solution was basic. The resulting mixture was extracted with 30 mL of dichloromethane. The extract was washed with two 10-mL portions of water, dried (Na_2SO_4), and concentrated in vacuo to give 102.3 mg of a brown oil. The oil was chromatographed over 11 g of silica gel (eluted with methanol (12% ammonia)–chloroform, 1.5:98.5) to give 59.6 mg (48%) of amino ketone **19** as a yellow oil and 33.1 mg (27%) of a mixture of **19** and **20**.

2-Ethyl-2-[*rel*-(2*R*,6*S*,9*S*)-2-propyl-1-azabicyclo[4.3.0]nonan-9-yl]-1,3-dithiacyclohexane (21) and 2-Ethyl-2-[*rel*-(2*R*,6*S*,9*R*)-2-propyl-1-azabicyclo[4.3.0]nonan-9-yl]-1,3-dithiacyclohexane (22). Following method B of the preparation of amino ketone **19**, vinylogous amide **18** (659 mg, 2.8 mmol) was reduced with 191 mg (3.03 mmol) of sodium cyanoborohydride and oxidized with 1.03 mL of Jones reagent to give 637 mg of a brown oil. To this oil in 9 mL of dry chloroform was added 1.02 g (9.43 mmol) of 1,3-propanedithiol in one portion. Hydrogen chloride was bubbled through the resulting solution for 10 min. The resulting turbid solution was allowed to stand at room temperature for 3 h and partitioned between 30 mL of saturated sodium bicarbonate solution and 70 mL of dichloromethane. The aqueous phase was extracted with two 15-mL portions of dichloromethane, and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give 0.902 g of a yellow oil. This oil was chromatographed over 95 g of silica gel (eluted with methanol (12% ammonia)–chloroform, 1:99) to give 553 mg (60%) of thioketal **21** as a pale-orange oil [IR ($CHCl_3$) 2940, 2870 cm^{-1}; NMR ($CDCl_3$) δ 0.73–2.35 (m, 20 H), 2.35–3.27 (m, 7 H, NCH, SCH_2); ^{13}C NMR (C_6D_6) δ 9.66 (q), 14.90 (q), 19.86 (t), 21.21 (t), 24.08 (t), 25.49 (t), 26.17 (t), 26.26 (t), 28.26 (t), 31.36 (t), 32.43 (t), 33.15 (t), 45.10 (t), 52.97 (d), 53.89 (s), 54.86 (d), 55.64

(d); mass spectrum, *m/e* (relative intensity) 327 (2), 284 (28), 166 (100), 122 (26); exact mass calcd for $C_{18}H_{33}NS_2$ *m/e* 327.2054, found *m/e* 327.2049] and 235 mg (26%) of thioketal **22** as a pale-yellow oil [IR ($CHCl_3$) 2940, 2870 cm^{-1}; NMR ($CDCl_3$) δ 0.70–2.47 (m, 26 H), 2.47–3.40 (m, 7 H, NCH, SCH_2); ^{13}C NMR (C_6D_6) δ 9.76 (q), 14.56 (q), 19.95 (t), 20.73 (t), 23.64 (t), 25.44 (t), 26.07 (t), 26.22 (t), 27.19 (t), 30.10 (t), 32.48 (t), 35.44 (t), 47.58 (t), 51.95 (d), 53.99 (s and d), 55.00 (d); mass spectrum, *m/e* (relative intensity) 327 (2), 284 (33), 166 (100), 122 (12); exact mass calcd for $C_{18}H_{33}NS_2$ *m/e* 327.2054, found *m/e* 327.2062].

***rel*-(2*R*,6*S*,9*R*)-9-Butyl-2-propyl-1-azabicyclo[4.3.0]nonane (2).** A solution of 132 mg (0.405 mmol) of thioketal **21** in 5 mL of ethylamine in a test tube was cooled in a dry ice–carbon tetrachloride bath with the test tube stoppered with a rubber stopper. Lithium (60.0 mg) was cut into the test tube in small pieces. The test tube was stoppered and cooled with constant shaking, and the pressure was released periodically. When the reaction mixture remained blue, it was poured carefully into 10 mL of water. The aqueous solution was extracted twice with dichloromethane (50 mL total). The combined organic layers were dried (Na_2SO_4), concentrated in vacuo, and chromatographed over 11 g of silica gel with methanol (12% ammonia)–chloroform (2:98) as eluent to give 54.2 mg (60%) of **2** as a pale-yellow oil: IR ($CHCl_3$) 2970, 2940, 2880 cm^{-1}; NMR ($CDCl_3$) 0.67–2.00 (m, 26 H), 2.20–2.77 (br s, 2 H, NCH), 2.77–3.17 (br s, 1 H, NCH); ^{13}C NMR (C_6D_6) δ 14.37, 14.66, 20.05, 21.31, 23.64, 28.45, 28.79, 30.44, 33.21, 33.45, 52.72, 56.41, 58.40; mass spectrum, *m/e* (relative intensity) 223 (5), 180 (100), 166 (93), 122 (5); exact mass calcd for $C_{15}H_{29}N$ *m/e* 223.2300, found *m/e* 223.2304.

***rel*-(2*R*,6*S*,9*S*)-9-Butyl-2-propyl-1-azabicyclo[4.3.0]nonane (3).** A solution of 220 mg of thioketal **22** in 8.0 mL of ethylamine in a 50-mL pear-shaped flask was cooled in a dry ice–carbon tetrachloride bath with the flask stoppered with a rubber stopper. Lithium (100 mg) was cut into the flask in small pieces. The flask was stoppered and cooled with constant shaking and the pressure was released periodically. When the reaction mixture stayed blue, it was poured carefully into 20 mL of water. The resulting mixture was extracted with dichloromethane (80 mL total). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to give 146 mg of a pale-yellow oil. This oil was chromatographed over 10 g of silica gel (eluted with 1:99 methanol (12% ammonia)–chloroform) to give 34 mg (23%) of indolizidine **3** as a yellow oil, homogenous by GLC (6 ft × $^1/_8$ in. OV-101, 190 °C): IR ($CHCl_3$) 2960, 2940, 2870 cm^{-1}; NMR ($CDCl_3$) δ 0.73–2.47 (m, 26 H), 2.53–3.47 (m, 3 H); ^{13}C NMR (C_6D_6) δ 14.47, 14.56, 20.10, 20.73, 23.64, 27.72, 28.79, 28.94, 29.76, 35.54, 36.27, 52.89, 54.81, 58.50; mass spectrum, *m/e* (relative intensity) 223 (6), 180 (94), 166 (100); exact mass calcd for $C_{15}H_{29}N$ *m/e* 223.2300, found *m/e* 223.2296.

Ethyl [*rel*-(2*R*,6*S*)-2-Propyl-1-azabicyclo[4.3.0]nonan-9-ylidene]acetate (23). To a solution of 5.23 g (26.5 mmol) of thiolactam **17** in 90 mL of dry ether was added 5.57 g (33.4 mmol) of ethyl bromoacetate in one portion and the resulting solution was stirred under nitrogen at room temperature for 37 h. The ether layer was removed with a pipet and concentrated in vacuo to give a pale-yellow oil. The oil was dissolved in 130 mL of dry chloroform and the mixture returned to the original reaction vessel. The reaction mixture was cooled in an ice bath followed by sequential addition of 8.94 g (26.5 mmol) of triphenylphosphine and 7.4 mL (53.2 mmol) of triethylamine. The resulting solution was stirred at room temperature under nitrogen for 30 min and concentrated in vacuo. The residual solid was triturated sequentially with 100- and 500-mL portions of ethyl acetate–hexane (1:9). The combined extracts were concentrated in vacuo. The residual oil was stirred with 50 mL of ethyl acetate–hexane (1:9) and filtered through Celite. The filtrate was concentrated in vacuo, and excess ethyl bromoacetate was removed under a pressure of 0.1 mm at room temperature to afford 7.47 g of an orange oil that contained about 0.62 g of triphenylphosphine sulfide and 6.85 g (100%) of vinylogous urethane **23** by NMR analysis. This crude product was used directly in the next reaction. A portion of the crude **23** was chromatographed over silica gel (eluted with ethyl acetate–hexane, 1:9) to give pure **23** as a pale-yellow oil: IR ($CHCl_3$) 1675, 1590 cm^{-1}; NMR ($CDCl_3$) δ 0.70–3.83 (m with t, J = 7 Hz, at 1.23, 22 H, CH_3, CH_2), 4.07 (q, J = 7 Hz, 2 H, OCH_2), 4.5 (s, 1 H, =CH); mass spectrum, *m/e* (relative intensity) 251 (19), 236 (8), 222 (10), 209 (67), 208 (31), 206 (36), 178 (19), 164 (33), 162 (17), 136 (100); exact mass calcd for $C_{15}H_{25}NO_2$ *m/e* 251.1885, found *m/e* 251.1892.

Ethyl [*rel*-(2*R*,6*S*,9*S*)-2-Propyl-1-azabicyclo[4.3.0]nonan-9-yl]acetate (24) and Ethyl [*rel*-(2*R*,6*S*,9*R*)-2-Propyl-1-azabicyclo[4.3.0]nonan-9-yl]acetate (25). To a solution of 7.47 g (26.5 mmol) of crude vinylogous urethane **23** in 55 mL of dry methanol was added a trace of bromocresol green followed by 1.68 g (26.6 mmol) of sodium cyanoborohydride. A 1.14 N methanolic hydrochloric acid solution (40 mL total) was added dropwise until the reaction mixture maintained a yellow color. The resulting solution was poured into 140 mL of 0.2 N aqueous sodium hydroxide and extracted with two 200-mL portions of dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give 8.23 g of a colorless liquid with an immiscible blue oil at bottom. This mixture was chromatographed over 500 g of silica gel (eluted with methanol (5% ammonia)–chloroform, 1.5:98.5, followed by methanol (2% ammonia)–chloroform, 8:92) to give 3.39 g (50%) of amino ester **24** as a colorless liquid: IR ($CHCl_3$) 1715 cm^{-1}; NMR ($CDCl_3$) δ 0.76–2.00 (m with t, J = 7 Hz, at 1.27, 2 OH, CH_3, CH_2), 2.00–2.76 (m, 3 H, $COCH_2$, NCH), 2.76–3.33 (m, 2 H, NCH), 4.12 (q, J = 7 Hz, 2 H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 14.32 (q), 14.47 (q), 19.27 (t), 20.88 (t), 23.50 (t), 27.96 (t), 28.79 (t), 29.86 (t), 32.58 (t), 39.32 (t), 52.82 (d), 54.96 (d), 56.02 (d), 60.15 (t), 172.64 (s); mass spectrum, *m/e* (relative intensity) 253 (3), 210 (100), 166 (30), 122 (52); exact mass calcd for $C_{15}H_{27}NO_2$ *m/e* 253.2042, found *m/e* 253.2050.

Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74. Found: C, 71.04; H, 10.49.

Continued elution gave 1.81 g (27%) of amino ester **25** as a colorless liquid: IR ($CHCl_3$) 1715 cm^{-1}; NMR ($CDCl_3$) δ 0.67–2.83 (m with t, J = 7 Hz, at 1.23, 23 H, CH_3, CH_2), 2.83–3.67 (m, 2 H, NCH), 4.08 (q, J = 7 Hz, 2 H, OCH); ^{13}C NMR ($CDCl_3$) δ 14.27 (q), 19.37 (t), 20.34 (t), 23.40 (t), 27.48 (t). 18.94 (t), 29.18 (t), 25.25 (t), 41.85 (t), 52.63 (d), 54.67 (d), 55.68 (d), 60.06 (t), 172.83 (s); mass spectrum, *m/e* (relative intensity) 253 (5), 210 (100), 166 (40), 122 (45); exact mass calcd for $C_{15}H_{27}NO_2$ *m/e* 253.2042, found *m/e* 253.2050.

β-[*rel*-(2*R*,6*S*,9*S*)-2-Propyl-1-azabicyclo[4.3.0]nonan-9-yl]ethanol (26). To a mixture of 274 mg (7.22 mmol) of lithium aluminum hydride in 35 mL of dry tetrahydrofuran was added dropwise 1.20 g (4.75 mmol) of amino ester **24** in 35 mL of dry tetrahydrofuran over a period of 25 min. The mixture was stirred under nitrogen for an additional 15 min at room temperature followed by sequential addition of 1.4 mL of water, 1.4 mL of 3 N sodium hydroxide solution, 2.8 mL of water, a portion of magnesium sulfate, and 28 mL of ether. The resulting mixture was filtered through Celite and concentrated in vacuo to give 0.971 g (97%) of crude amino alcohol **26** as a pale-yellow oil, homogeneous by thin-layer chromatography (alumina; ethyl acetate–hexane, 7:3): IR ($CHCl_3$) 3200 (br) cm^{-1}; NMR ($CDCl_3$) δ 0.60–2.77 (m, 20 H), 2.77–3.43 (br s, 2 H, NCH), 3.62 (td, J = 11, 4 Hz, 1 H, OCH), 4.02 (dt, J = 11, 3 Hz, 1 H, OCH); mass spectrum *m/e* (relative intensity) 211 (3), 168 (100), 166 (34), 124 (8), 122 (6); exact mass calcd for $C_{13}H_{25}NO$ *m/e* 211.1936, found *m/e* 211.1941.

β-[*rel*-(2*R*,6*S*,9*R*)-2-Propyl-1-azabicyclo[4.3.0]nonan-9-yl]ethanol (27). To a mixture of 29.7 mg (0.782 mmol) of lithium aluminum hydride in 4 mL of dry tetrahydrofuran was added 130 mg (0.513 mmol) of amino ester **25** in 4 mL of dry tetrahydrofuran over a period of 5 min. The mixture was stirred at room temperature for 15 min followed by sequential addition of 3 drops of water, 3 drops of 3 N aqueous sodium hydroxide, 6 drops of water, magnesium sulfate, and 3 mL of ether. The resulting mixture was filtered through Celite and concentrated in vacuo to afford 104 mg (96%) of crude amino alcohol **27** as a pale-yellow oil, homogenous by thin-layer chromatography (alumina; ethyl acetate–hexane, 7:3): IR ($CHCl_3$) 3190 (br) cm^{-1}; NMR ($CDCl_3$) δ 0.70–2.90 (m, 20 H, CH_3, CH_2, NCH), 2.90–4.13 (m, 4 H, NCH, OCH_2), 5.60–6.60 (br s, 1 H, OH); mass spectrum, *m/e* (relative intensity) 211 (5), 210 (2), 168 (100), 166 (46), 124 (6), 122 (6); exact mass calcd for $C_{13}H_{25}NO$ *m/e* 211.1936, found *m/e* 211.1929.

***rel*-(1*R*,4*S*,7*S*,11*R*)-11-Propyl-1-azatricyclo[5.4.0.0^{1,4}]undecane Tetrafluoroborate (28).** To a solution of 81 mg (0.43 mmol) of amino alcohol **26** in 0.5 mL of dry dichloromethane cooled in an ice bath under argon was added 0.15 mL of triethylamine in a single portion followed by the addition of a

solution of 55 mg (0.48 mmol) of methanesulfonyl chloride in 0.5 mL of dichloromethane. The resulting solution was stirred at 0 °C for 7 min, diluted with 15 mL of dichloromethane, and poured into 5 mL of a mixture of equal parts of 10% potassium hydroxide aqueous solution and saturated sodium chloride aqueous solution. The aqueous phase was extracted with 5 mL of dichloromethane, and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to give 110 mg of a white solid. This solid was dissolved in 0.5 mL of methanol and stirred with an aqueous solution of 1.4 g sodium tetrafluoroborate (12.7 mmol) in 6 mL of water for 1 h. The resulting solution was extracted with chloroform (2 × 10 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give 102 mg of a white solid. This material was recrystallized from ether–dichloromethane (3:2) to give 74 mg (61%) of the tetrafluoroborate salt **28** as white crystals: mp 162–163 °C; IR ($CHCl_3$) 3040, 2960, 2880, 1460 cm^{-1}; NMR ($CDCl_3$) δ 0.85–2.50 (m, 18 H), 2.50–3.60 (m with qu at 2.97, J = 11 Hz, 2 H, NCH, methylene CH), 3.60–4.60 (m, with qu at 4.27, J = 10 Hz, 3 H, NCH), 4.60–5.00 (m, 1 H, NCH); ^{13}C NMR ($CDCl_3$) δ 13.79 (q), 17.53 (t), 19.42 (t), 20.10 (t), 21.26 (t), 22.33 (t), 27.04 (t), 27.58 (t), 30.15 (t), 35.00 (t), 64.13 (d), 65.88 (d), 71.66 (d).

Anal. Calcd for $C_{13}H_{24}NBF_4$: C, 55.50; H, 8.60. Found: C, 54.61; H, 8.83.

***rel*-(1*S*,4*R*,7*S*,11*R*)-11-Propyl-1-azatricyclo[5.4.0.0^{1,4}]undecane Tetrafluoroborate (29).** To a solution of 78 mg (0.37 mmol) of amino alcohol **27** in 0.43 mL of dry dichloromethane cooled in an ice bath under argon was added 0.13 mL (0.93 mmol) of triethylamine in one portion followed by the addition of a solution of 47 mg (0.41 mmol) of methanesulfonyl chloride in 0.43 mL of dichloromethane. The resulting solution was stirred at 0 °C for 7 min, diluted with 20 mL of dichloromethane, and poured into 4 mL of a mixture of equal parts of 10% potassium hydroxide aqueous solution and saturated sodium chloride aqueous solution. The aqueous phase was extracted with 5 mL of dichloromethane, and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give 92 mg of a yellow solid. This material was dissolved in 0.4 mL of methanol and stirred with a solution of 1.2 g (10.9 mmol) of sodium tetrafluoroborate in 4 mL of water for 1 h. The resulting solution was extracted with dichloromethane (2 × 15 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated to give 90 mg (86%) of the tetrafluoroborate salt **29** as a yellow oil: IR ($CHCl_3$) 3040, 2960, 2880, 1470 cm^{-1}; NMR ($CDCl_3$) δ 0.80–3.40 (m, 19 H), 3.40–4.40 (m, 5 H), 4.70–5.07 (m, 1 H, NCH); ^{13}C NMR ($CDCl_3$) δ 13.74 (q), 15.44 (t), 19.57 (t), 20.34 (t), 22.53 (t), 25.78 (t), 29.94 (t), 30.44 (t), 56.66 (t), 63.11 (d), 66.66 (d), 74.57 (d).

Formation of Amino Ketone 19 via Grignard Addition to Amino Ester 24. To a solution of 97 mg (0.38 mmol) of amino ester **24** in 0.4 mL of dry ether under argon was added dropwise 1.5 mL of a solution of 1.28 M (5 equiv) ethylmagnesium bromide in ether. The resulting solution was stirred at room temperature for 6 h and transferred via syringe into a vigorously stirred mixture of 15 mL of dichloromethane, 10 mL of water, and approximately 5 g of ice. The resulting mixture was diluted with 30 mL of dichloromethane and separated. The aqueous phase was extracted with two 10-mL portions of dichloromethane, and the combined organic layers were dried and concentrated in vacuo to give 77 mg of a pale-yellow oil. This material was chromatographed over 8 g of silica gel [eluted with methanol (2% concentrated ammonium hydroxide)–chloroform; 8:92] to give 59 mg (65%) of a pale-yellow oil, which was identical by NMR and TLC [silica gel, methanol (2% concentrated ammonium hydroxide)–chloroform; 12:88] with amino ketone **19** prepared as described above.

Formation of Amino Ketone 20 via Grignard Addition to Amino Ester 25. To a solution of 104 mg (0.41 mmol) of amino ester **25** in 0.4 mL of dry ether under argon was added dropwise 1.5 mL of a 1.278 M ethylmagnesium bromide in ether (4.7 equiv). The resulting solution was stirred at room temperature for 8 h and transferred via syringe into a vigorously stirred mixture of 10 mL of dichloromethane, 10 mL of water, and about 5 g of ice. The resulting mixture was diluted with 30 mL of dichloromethane and separated. The aqueous phase was extracted with two 10-mL portions of dichloromethane, and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give 82 mg of a pale-yellow oil, which was a mixture of amino ketone **20** and unreacted amino ester **25** by NMR, IR, and TLC [silica gel, methanol (2% concentrated ammonium hydroxide)–chloroform, 12:88; alumina, ethyl acetate–hexane, 1:9]. Attempts to purify this crude material by chromatography over 10 g of neutral activity III alumina (eluted with ethyl acetate–hexane, 2:98) resulted in isomerization of amino ketone **20** to a mixture of **20** and **19**. Signals due to **20** were visible at δ 0.70–2.80 and δ 3.00–3.80 (m, 3 H, NCH) in NMR spectra ($CDCl_3$) of the crude product mixture.

Acknowledgment. We thank Mr. Richard Weisenberger for recording mass spectra at The Ohio State University Chemical Instrument Center. Financial support from the National Institutes of Health (GM 27647-02) is gratefully acknowledged.

Registry No. **2**, 83024-10-6; **3**, 83024-11-7; **7**, 75534-05-3; **8**, 78688-77-4; **9**, 78688-79-6; **10**, 82979-13-3; **11**, 82979-14-4; **12**, 78167-73-4; **13**, 82979-15-5; **15**, 82979-16-6; **16**, 83024-07-1; **17**, 82979-17-7; **18**, 82979-18-8; **19**, 82979-19-9; **20**, 83024-08-2; **21**, 82979-20-2; **22**, 83024-09-3; **23**, 78167-66-5; **24**, 82979-21-3; **25**, 83024-12-8; **26**, 82979-22-4; **27**, 83024-13-9; **28**, 82979-24-6; **29**, 83024-15-1; 1-bromo-2-butanone, 816-40-0.

Reactivity of Tetracyanoethylene Oxide toward Heteroaromatic Compounds. Synthesis and Structure of Heterocyclic Dicyanomethylides

Enrique Diez-Barra and Maria del Carmen Pardo*

Departamento de Quimica Orgánica, Facultad de Ciencias Quimicas, Universidad Complutense, Madrid (3), Spain

José Elguero

Instituto de Quimica Médica, CSIC, Juan de la Cierva 3, Madrid (6), Spain

Received February 12, 1982

Tetracyanoethylene oxide (TCNEO) was allowed to react with 17 heterocyclic derivatives, mainly azoles. Only in ten cases the reaction affords the corresponding dicyanomethylide. The structure of these compounds was established by IR and ^1H NMR spectroscopies. The reactivity of heterocycles toward TCNEO increases with basicity and decreases with steric hindrance. A bidimensional plot of our results and those of the literature shows a clear frontier between reactive and unreactive heterocycles.

Tetracyanoethylene oxide (TCNEO) is a powerful and interesting reagent. Contrary to normal epoxides, TCNEO is not attacked by electrophilic reagents because of the presence of the strong electron-withdrawing cyano groups, but, for this same reason, it easily reacts with nucleophlic reagents.[1] Linn et al.[1-3] have examined the reactivity of

0022-3263/82/1947-4409$01.25/0