The Reaction of α-Nitro-ω-haloalkanes with Imines. Synthesis of 3-Nitropyrrolidines and 3-Nitropiperidines

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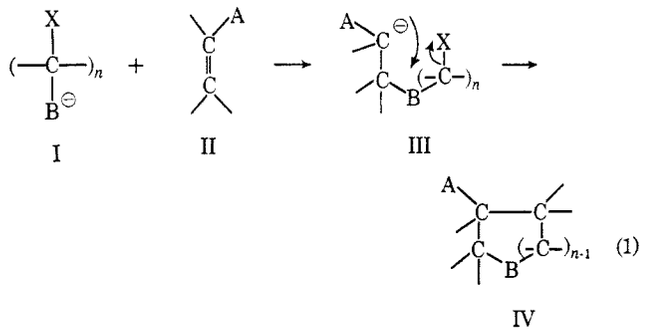
The reaction of 1-nitro-4-bromobutane and 1-nitro-3-chloropropane with imines has been found to lead to the formation of piperidines and pyrrolidines. The reaction course is envisaged as passing through the anion of a halonitroalkane which is trapped by reaction with imine, thereby leading to a haloamine which eventually cyclizes to a heterocyclic system.

The synthesis of nitropyrrolidines and nitropiperidines in general has not been an area of productive interest in the literature of organic chemistry. Apparently only N-nitro derivatives,[2] formed by the action of dinitrogen tetroxide or nitric acid–acetic anhydride mixtures on cyclic secondary bases, are known. We developed interest in the synthesis of 3-nitroheterocyclic amines as a method of general annelation of imines and as general synthesis of substituted pyrrolidines and piperidines.

A previous report[3] from these laboratories was concerned with the description of a sequence referred to as "Michael alkylation," a generalized depiction of ring synthesis which depends upon the spontaneous trapping of a molecule, *e.g.*, I, which possesses both nucleophilic and electrophilic reactivity, by a substrate, *e.g.*, II, of competing electrophilicity, the trapping process being followed by an intramolecular alkylation (III → IV) completing ring formation. This whole sequence is represented schematically in eq 1. In

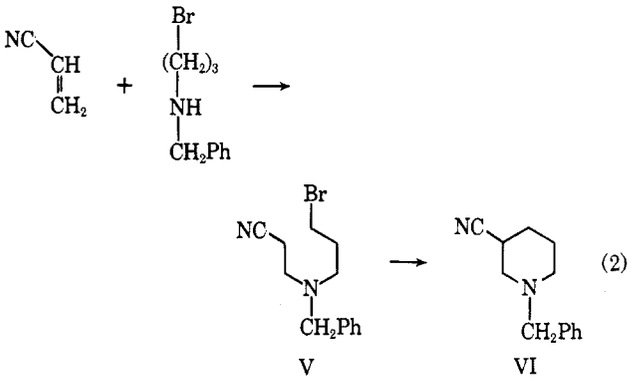


I II III IV (1)

X = halogen, etc.; B = electronegative atom; A = cyano, nitro, carboxylic ester groups, etc.

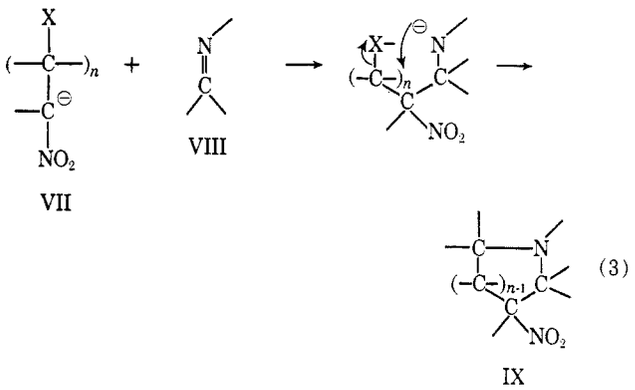
certain cases where a haloamine, I (B = NHR) reacts, the intermediate III is unchanged but may be caused to cyclize by addition of a strong base. This process has been exemplified by the trapping of N-benzyl-3-bromopropylamine with acrylonitrile giving the tertiary amine (V) which is caused to cyclize by potassium *t*-butoxide to the stable 3-cyano-1-benzylpiperidine (VI)[3] (eq 2).

In a continuation of our developing interest in the practicality of using substrates of "ambiphilic"[4] character in the synthesis of cyclic structures, the

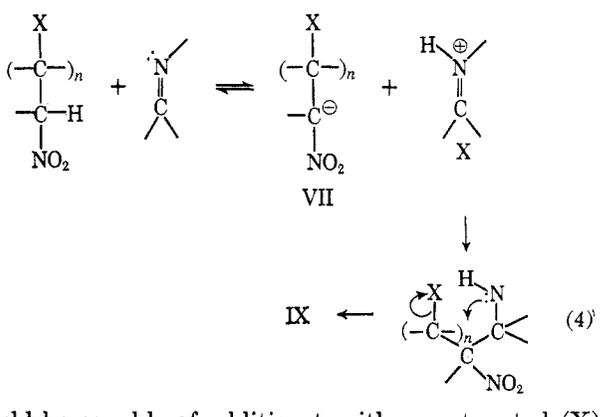


V VI (2)

possibility of intercepting nitroalkyl halide anions (VII) by imines (VIII) before detrimental fragmentation or cyclization of the halo anion occurred was examined; in the former event, a heterocycle (IX) was eventually formed (see eq 3). Under actual experimental conditions no effort was made to preform the anion; the basic quality of the imine would ensure the equilibrium between the anion VII and the immonium ion (X) (eq 4) with the expectation that the anion VII



VII VIII IX (3)



VII IX (4)

would be capable of addition to either protonated (X) or unprotonated (VIII) imine. As indicated the

(1) To whom inquiries may be addressed: The Squibb Institute for Medical Research, New Brunswick, N. J. 08903.

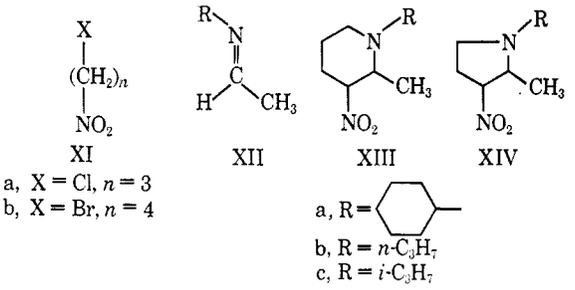
(2) W. D. Emmons, A. S. Pagano, and T. E. Stevens, *J. Org. Chem.*, **23**, 311 (1958); W. J. Chute, G. E. Dunn, J. W. MacKenzie, G. S. Myers, G. N. R. Smart, J. W. Suggitt, and G. F. Wright, *Can. J. Res.*, **26B**, 114 (1948).

(3) J. E. Dolfini and D. M. Dolfini, *Tetrahedron Lett.*, No. 31, 2103 (1964).

(4) Because of the awkward problem of referring to the general class of compounds which might be and have been involved as substrates in this type of ring synthesis, we use the term ambiphile to denote those reactive and unstable moities sharing a nucleophilic head and electrophilic tail.

ambiphilic halonitroalkyl anion (VII) once generated would not be expected to be indefinitely stable and internal carbon or oxygen alkylation and/or fragmentation processes might be anticipated.

Initial studies involved the reaction of 1-nitro-3-chloropropane[5] and 1-nitro-4-bromobutane with several representative aldimines, which were conveniently accessible by the procedure of Tiollais[6] by direct reaction of aldehydes with primary amines. The basic quality of the imine would seem to obviate a need for added base since Michael reactions of nitroalkanes can be catalyzed by amines.[7]



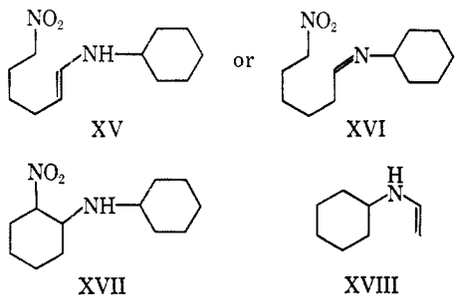
XI XII XIII XIV

a, X = Cl, n = 3
b, X = Br, n = 4

a, R =
b, R = n-C_3H_7
c, R = i-C_3H_7

The reaction of N-ethylidenecyclohexylamine (XIIa) with 4-bromo-1-nitrobutane (XIb) in benzene at room temperature for 16 hr provided a basic fraction upon work-up which corresponded to a 60% yield of 3-nitro-2-methyl-1-cyclohexylpiperidine (XIIIa). Evaporative distillation[8] was accompanied by some decomposition, but provided a sample of the pure amine. The identity of the material was indicated by the ir spectrum (no absorption in the 2.8–3.0-μ region and a band at 6.47 μ due to a nitro group). Combustion analysis was compatible with a molecular formula of $C_{12}H_{22}N_2O_2$. A vapor-pressure osmometer determination indicated mol wt 229 (calcd 226). The mass spectrum of the material gave a molecular ion of m/e 226. The pmr spectrum allowed identification of a doublet at 1.15 ppm of a C-methyl group and a multiplet at 4.3 ppm ascribed to a hydrogen α to the nitro group.

Alternative structures, *i.e.*, XV, XVI, and XVII, which might arise through isomerization of the imine

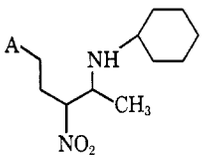


XV or XVI

XVII XVIII

to the enamine form XVIII, followed by reaction with the nitrohalobutane, are simply incompatible with the collection of spectral data.

The yield of product was not appreciably altered by carrying the reaction out in the presence of an equivalent of triethylamine. However, decreasing the reaction time to 5 hr resulted in the isolation of the acyclic intermediate, XIXa, as the hydrochloride salt, in 38%



XIXa, A = $-CH_2Br$
b, A = $-CO_2CH_3$

yield as well as 30% of the substituted piperidine (XIIIa). The salt proved to be extremely difficult to purify since it was insoluble in nearly all organic solvents and water. It did crystallize with difficulty from dimethyl sulfoxide, but an analytically pure sample could not be obtained. The ir spectrum showed strong secondary amine salt and nitro group absorptions. However, the related material (XIXb), isolated as the HCl salt, which was prepared by reaction of ethyl 4-nitrobutyrate with the imine XIIa in benzene in the presence of triethylamine, possessed a notably similar ir spectrum with additional carboxyl absorption and gave a satisfactory analysis. The acyclic material XIXa is not found after longer reaction times.

The rate of these ambiphilic additions was increased by conducting the reaction in dimethylformamide (see Experimental Section).

Similar reactions of 1-bromo-1-nitrobutane with N-ethylidine-n-propylamine provided a 68% crude yield of the product XIIIb, and a 58% yield of the pure compound, bp 70–75° (0.1 mm). It seemed that the greater the volatility of the particular nitroamine, the less decomposition occurred owing to lower temperature of distillation (where products of low volatility are obtained, isolation as a salt may be preferred). The physical data on this and following compounds can be found in the Experimental Section.

N-Ethylideneisopropylamine was also converted into the corresponding nitropiperidine XIIIc by this reaction.

The reaction is relatively free from deleterious side reactions, and it would be expected that improved yields of these nitropiperidines can be obtained by suitable adjustment of reaction conditions.

The use of 1-nitro-3-chloropropane proved to be similarly successful. Thus the reaction of 1-nitro-3-chloropropane with an equimolar amount of N-ethylidenecyclohexylamine in benzene gave rise to a 65% yield of XIVa. A tertiary aminonitroalkyl compound was indicated by the infrared spectrum. The pmr spectrum revealed a doublet at 1.2 ppm and a multiplet at 4.5 ppm. The mass spectrum showed a molecular ion at m/e 212.

The reaction of N-ethylideneisopropylamine and N-ethylidene-n-propylamine gave 40% of XIVb and 43% of XIVc, respectively, the products being characterized by ir, pmr, and mass spectra, as well as solid derivatives.

Benzalaniline failed to react with either of the halonitroalkanes studied here under a variety of conditions presumably owing to the decreased ability of the aromatic imine to participate in either addition or alkylation reactions.

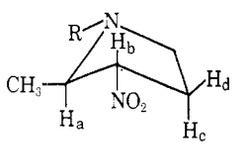
(5) Commercially available from K & K Laboratories, Inc., Plainview, N. Y.

(6) R. Tiollais, *Bull. Soc. Chim. Fr.*, **14**, 708 (1947).

(7) *Cf.* E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, **10**, 179 (1959).

(8) Because of the thermal instability of these nitroamines, crude yields before distillation are probably more indicative of the extent of ambiphilic cycloaddition.

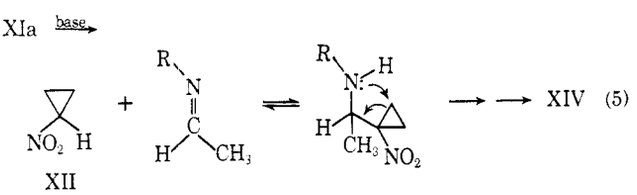
The pmr spectra of the compounds were largely unexceptional. The ring methyl absorptions appeared at about δ 1.25, with coupling to the adjacent methine hydrogen, J = ~6.5 cps. The methine hydrogen adjacent to the nitro group absorbed in the region of δ 4.0–4.3. The absorption of this hydrogen in the piperidine system XIII is not well defined as to pattern, whereas the methine absorption in the pyrrolidine system XIV appears distinctly in all cases as overlapping doublets of triplets. A consideration of the pertinent hydrogens in compound XIV[9] makes it apparent that H_d,H_c have different electronic environ-



XIV

ments and form widely different dihedral bond angles with H_b. However, it also becomes apparent that, whereas H_a and H_c are in clearly different electronic environments, they form similar, if not identical, dihedral bond angles with H_b. Whereas a more complex splitting of H_b would *a priori* be expected owing to coupling with three chemically nonequivalent vicinal protons, the comparatively simple spectra observed may be explained if $J_{H_aH_b} = J_{H_cH_b}$, resulting in the splitting of the H_b signal into a triplet. The observed splitting is 5.0 cps, consistent with a dihedral bond angle, as seen from a model, of about 120°.[10] The observed coupling between H_b and H_d is 7.5 cps, consistent with a dihedral bond angle of about 0°.[10] While this analysis is in accord with the observations, it is to be recognized that the interpretations are limited by the sparse data involved.

In the several examples of nitropyrrolidine formations our inability to isolate an acyclic intermediate comparable with that found in the piperidine synthesis may simply be a reflection of the greater ease of cyclization in the formation of five- *vs.* six-membered rings or may be the result of a somewhat different reaction path. Owing to the rapid rate of cyclopropane formation it may be anticipated that the anion derived from 1-nitro-3-chloropropane would cyclize rapidly to provide nitrocyclopropane. Indeed this reaction has been reported previously[11] under basic conditions and could easily be manifest under the conditions of our reactions (see eq 5). The nucleophilic expansion



XII (5)

of the aminomethylnitrocyclopropane intermediate is analogous to the general type of intermolecular ring opening of "activated" cyclopropanes as exemplified by the reaction of 1,1-dicarbethoxycyclopropane with malonic ester anion.[12]

It is apparent that a novel method for heterocyclic formation has been found of potential generality. In the cases described here a heretofore unknown class of nitropyrrolidines and nitropiperidines has been entered upon. The ramifications of the method and elucidation of the suggested mechanisms await further study.

Experimental Section[13]

1-Bromo-4-nitrobutane (XIb).[14]—To a mixture of 10.6 g (0.15 mol) of sodium nitrite and 600 ml of dimethylformamide (freshly distilled from calcium hydride) was added rapidly from a dropping funnel 100 g (0.463 mol) of 1,4-dibromobutane. The mixture was stirred slowly for 5 hr. After 3 hr the solution was dark orange and bromine fumes gradually appeared; after 5 hr the reaction mixture was poured into 1 l. of ice and water, layered with hexane. The water layer was extracted three times with hexane. The hexane solution was dried with magnesium sulfate, and the solvent was removed under reduced pressure. The product distilled at 120–124° (18 mm), 4 g (15%) of product being obtained: ir, λ 6.50 μ; pmr, 4.5 (triplet), 3.5 (triplet), 2.1 ppm (multiplet).

Anal. Calcd for $C_4H_8NO_2Br$: C, 26.39; H, 4.45; N, 7.69; Br, 43.90. Found: C, 26.73; H, 4.44; N, 7.57; Br, 44.43.

N-Cyclohexyl-2-methyl-3-nitropiperidine (XIIIa). Method 1.—A mixture of 2 g (11 mmol) of 1-bromo-4-nitrobutane and 1.35 g (11 mmol) of N-ethylidenecyclohexylamine[6] in 20 ml of dry benzene was stirred under nitrogen overnight at room temperature. The benzene solution was extracted with 10% hydrochloric acid. The acid was neutralized with saturated sodium bicarbonate, and the aqueous solution was extracted with benzene. The benzene layer yielded 1.5 g (60%) of crude product upon evaporation. The product was evaporatively distilled, at 80–110° (0.1 mm). N-Cyclohexyl-2-methyl-3-nitropiperidine [350 mg (14%)]was obtained: ir, λ_{max}^{film} 6.47 and 7.44 μ; pmr, 1.15 (doublet) and 4.3 ppm (multiplet). The mass spectrum indicated a molecular ion at m/e 226.

Anal. Calcd for $C_{12}H_{22}N_2O_2$: C, 63.68; H, 9.80; N, 12.38. Found: C, 63.97; H, 9.67; N, 12.20.

Method 2.—A solution of 1.5 g (8 mmol) of 1-bromo-4-nitrobutane in 5 ml of dry benzene was added dropwise to 1 g (8 mmol) of N-ethylidenecyclohexylamine and 0.8 g (8 mmol) of triethylamine in 10 ml of dry benzene. The mixture was stirred under nitrogen overnight. The basic fraction was isolated as in method 1. After being kept under vacuum for 4 hr to remove the triethylamine, the product weighed 1.2 g (64%).

The picrate was prepared in a yield of 1.94 g (53%). A recrystallization from ethanol gave the analytical sample, mp 177–178°.

Anal. Calcd for $C_{18}H_{25}N_5O_9$: C, 47.47; H, 5.53; N, 15.38. Found: C, 47.36; H, 5.32; N, 15.17.

Method 3.—A solution of 2 g (11 mmol) of 1-bromo-4-nitrobutane, 1.5 g (12 mmol) of N-ethylidenecyclohexylamine, 1.3 g (13 mmol) of triethylamine, and 20 ml of dry dimethylformamide was stirred under nitrogen for 5 hr. The mixture was poured into water and extracted with benzene. The basic fraction, isolated as in method 1, yielded 1.3 g (52%) of N-cyclohexyl-2-methyl-3-nitropiperidine.

2-Cyclohexylamino-3-nitro-6-bromohexane (XIXa).—A solution of 3 g (16 mmol) of 1-bromo-4-nitrobutane in 15 ml of dry benzene was added dropwise to a solution of 2 g (16 mmol) of N-ethylidenecyclohexylamine and 1.6 g of triethylamine in 15 ml of dry benzene. The solution was stirred for 5 hr. With the addition of 10% hydrochloric acid, a precipitate formed and

(9) The conformationally most stable isomer is expected to result from equilibrating reaction conditions; therefore only the "all-equatorial" form is considered.

(10) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(11) P. G. Bay, U. S. Patent 3,100,805; *Chem. Abstr.*, **60**, 421*d* (1964).

(12) R. W. Kierstead, R. P. Linstead, and B. C. L. Weedon, *J. Chem. Soc.*, 3016 (1952).

(13) All melting points are corrected; boiling points are uncorrected. Ir spectra were obtained on a Beckman IR-8 instrument. The proton magnetic resonance spectra were determined in deuteriochloroform (tetramethylsilane, internal standard) on a Varian Associates A-60 instrument; chemical shifts are reported in δ units. Molecular weights were determined from mass spectra obtained on a Perkin-Elmer-Hitachi spectrometer. The combustion analysis were graciously performed by Dr. C. S. Yeh.

(14) Procedure modification of N. Korblum, H. O. Larson, R. K. Blackwood, D. D. Mooberry, E. P. Olivetto, and G. E. Graham, *J. Amer. Chem. Soc.*, **78**, 1498 (1956).

was filtered off. Recrystallization from dimethyl sulfoxide gave 2.1 g (38%), mp 145–147°. The infrared spectrum (KBr) showed NH and NO_2 absorptions.

Anal. Clacd for $C_{12}H_{24}N_2O_2BrCl$: C, 41.8; H, 7.04; N, 8.14. Found: C, 44.04; H, 7.57; N, 8.23.

Also obtained from the reaction mixture was 1.1 g (30%) of the piperidine XIIIa.

2-Methyl-3-nitro-N-*n*-propylpiperidine (XIIIb).—A solution of 1 g (5.5 mmol) of 1-bromo-4-nitrobutane in 5 ml of dry benzene was added dropwise to a solution of 0.47 g (5.5 mmol) of N-ethylidene-*n*-propylamine[6] and 0.55 g of triethylamine in 5 ml of dry benzene. The reaction mixture was stirred overnight under nitrogen. The basic fraction, obtained in the usual manner, weighed 678 mg (68%). The product was evaporatively distilled at 70–75° (0.1 mm), and yielded 473 mg (56%) of 2-methyl-3-nitro-N-*n*-propylpiperidine: ir, λ_{max}^{film} 6.44 μ; pmr, (doublet) and 4.2 ppm (multiplet).

Anal. Calcd for $C_9H_{18}N_2O_2$: C, 58.03; H, 9.74; N, 15.04. Found: C, 58.24; H, 10.03; N, 14.53.

The picrate was made and recrystallized from ethanol, mp 136–138°.

Anal. Calcd for $C_{15}H_{21}N_5O_9$: C, 43.37; H, 5.10; N, 16.86. Found: C, 43.55; H, 5.44; N, 17.11.

N-Isopropyl-2-methyl-3-nitropiperidine (XIIIc).—A solution of 0.94 g (11 mmol) of N-ethylideneisopropylamine[6] in 10 ml of dry benzene was added dropwise to a solution of 2 g (11 mmol) of 1-bromo-4-nitrobutane and 1.1 g (9 mmol) of triethylamine in 10 ml of dry benzene. The reaction mixture was stirred overnight. The basic fraction, isolated in the usual manner, yielded 600 mg (30%). An evaporative distillation at 70–75° (0.5 mm) of this material yielded 450 mg (23%) of N-isopropyl-2-methyl-3-nitropiperidine: ir, λ_{max}^{film} 6.44 μ.

Anal. Calcd for $C_9H_{18}N_2O_2$: C, 58.03; H, 9.74; N, 15.04. Found: C, 57.83; H, 9.83; N, 14.82.

The picrate was prepared and recrystallized from acetonitrile, mp 165–167°.

Anal. Calcd for $C_{15}H_{21}N_5O_9$: C, 43.37; H, 5.10. Found: C, 43.51; H, 3.55.

2-Methyl-3-nitro-N-*n*-propylpyrrolidine (XIVb). Method 1.—A solution of 1 g (8 mmol) of 1-chloro-3-nitropropane in 5 ml of dry benzene was added dropwise to a solution of 0.69 g (8 mmol) of N-ethylidene-*n*-propylamine and 0.82 g (8 mmol) of triethylamine in 10 ml of dry benzene. The reaction mixture was stirred overnight. The basic fraction, separated in the usual manner, contained 643 mg (43%). Evaporative distillation at 62–90° (0.04 mm) gave 392 mg (28%) of 2-methyl-3-nitro-N-*n*-propylpyrrolidine: ir, λ_{max}^{film} 6.44 μ.

Anal. Calcd for $C_8H_{16}O_2N_2$: C, 55.79; H, 9.36. Found: C, 55.57; H, 9.29.

Method 2.—The reaction was run as in method 1 with the omission of the triethylamine. The basic fraction weighed 380 mg (27%). The picrate was prepared and recrystallized from ethanol yielding a derivative, mp 145.5–146.5°.

Anal. Calcd for $C_{14}H_{19}N_5O_9$: C, 41.90; H, 4.77. Found: C, 41.99; H, 5.28.

N-Isopropyl-2-methyl-3-nitropyrrolidine (XIVc). Method 1.—A solution of 1 g (8 mmol) of 1-chloro-3-nitropropane in 5 ml of dry benzene was added dropwise to a solution of 0.69 g of N-ethylideneisopropylamine and 0.82 g (8 mmol) of triethylamine in 15 ml of dry benzene. The mixture was stirred overnight. The basic fraction, isolated in the usual manner, contained 695 mg. The triethylamine was removed under reduced pressure, leaving 523 mg (37%). Evaporative distillation yielded 327 mg (23%) of N-isopropyl-2-methyl-3-nitropyrrolidine: pmr, 1.2 (doublet) and 4.6 ppm (multiplet).

Anal. Calcd for $C_8H_{16}N_2O_2$: C, 55.79; H, 9.39. Found: C, 55.72; H, 9.14.

Method 2.—The reaction was run as in method 1 with the omission of the triethylamine. The basic fraction contained 553 mg (41%). The product was evaporatively distilled and 110 mg (8.2%) of N-isopropyl-2-methyl-3-nitropyrrolidine was obtained. The picrate was prepared and recrystallized from ethanol, mp 172–173°.

Anal. Calcd for $C_{14}H_{19}N_5O_9$: C, 41.90; H, 4.77. Found: C, 42.01; H, 5.00.

N-Cyclohexyl-2-methyl-3-nitropyrrolidine (XIVa). Method 1.—A mixture of 1 g (8 mmol) of N-ethylidenecyclohexylamine, 1 g (8 mmol) of 1-chloro-3-nitropropane, and 0.82 g of triethylamine was stirred under nitrogen overnight in 15 ml of dry benzene. The basic fraction, isolated in the usual manner, contained the product as 1.1 g of an oil (65%). The product was evaporatively distilled and yielded 890 mg (52%) of N-cyclohexyl-2-methyl-3-nitropyrrolidine: ir, λ_{film} 6.43 μ; pmr, 1.2 (doublet) and 4.5 ppm (multiplet). The mass spectrum showed a molecular ion at 212.

Anal. Calcd for $C_{11}H_{20}N_2O_2$: C, 62.23; H, 13.20. Found: C, 62.33; H, 9.46; N, 13.28.

Method 2.—The reaction was run as in method 1 with the omission of the triethylamine. The basic fraction contained 948 mg (56%). The picrate was prepared and recrystallized from acetonitrile; 200 mg (12%) was obtained, mp 175–177°.

Anal. Calcd for $C_{17}H_{23}N_5O_9$: C, 46.26; H, 5.25. Found: C, 46.31; H, 5.41.

Methyl 4-Nitro-5-(cyclohexylamino)hexanoate (XIXb).—A solution of 2 g (13.6 mmol) of methyl 4-nitrobutyrate in 10 ml of dry benzene was added dropwise to a solution of 1.7 g (13.6 mmol) of N-ethylidenecyclohexylamine and 1.4 g (14 mmol) of triethylamine in 20 ml of dry benzene. The solution was stirred overnight. Hydrochloric acid (10%) was added to the benzene to wash out any triethylamine or cyclohexylamine. A precipitate formed which was not dissolved by the addition of more water. It was removed by filtration and recrystallized from dimethyl sulfoxide as white crystals, mp 147–152°. It proved to be the hydrochloride of the uncyclized methyl 4-nitro-5-(cyclohexylamino)hexanoate.

Anal. Calcd for $C_{13}H_{25}N_2O_4Cl$: C, 50.56; H, 8.16; N, 9.07. Found: C, 50.84; H, 8.33; N, 8.96.

Registry No.—XIb 16097-02-2; XIIIa, 16097-28-2; XIIIa picrate, 16097-29-3; XIIIb, 16097-30-6; XIIIb picrate, 16097-31-7; XIIIc, 16097-32-8; XIIIc picrate, 16097-33-9; XIVa, 16097-34-0; XIVa picrate, 16097-35-1; XIVb, 16097-36-2; XIVb picrate, 16097-37-3; XIVc, 16176-04-8; XIVc picrate, 16097-38-4; XIXa HCl, 16097-39-5; XIXb HCl, 16097-40-8.