Azo Compounds. The Oxidation of 2,6-Dicyano- and 2,6-Dicarboxamido-Substituted 1-Aminopiperidines[1]

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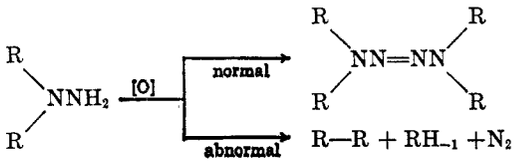
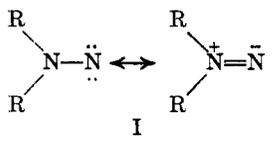
Oxidation of 1-amino-2,6-dicyanopiperidine and 1-amino-2,6-dicarboxamidopiperidine with mercuric oxide proceeds abnormally to form nitrogen and coupled and disproportionated products. Collapse of the intermediate nitrene may proceed *via* radical or ionic paths with considerable contribution from the former. Product analysis suggests that the direction of nitrene collapse is sterically governed, cyclization being preferred, and that ring closure is stereoselective, as previously reported.

The abnormal oxidation of 1,1-disubstituted hydrazines to coupled and olefinic products has been the subject of continuing studies (Scheme I).[3-6] A diazo-like

SCHEME I



intermediate I (an N-nitrene) has been postulated[7,8] to explain the formation of the observed products.



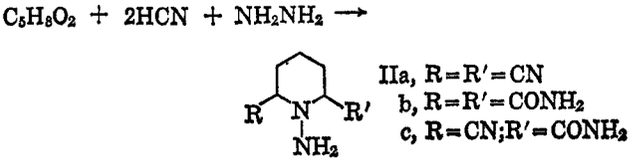
I

With 1-amino-2,6-dimethylpiperidine[3] normal oxidation was observed, while with 1-amino-2,6-dicyano-2,6-dimethylpiperidine abnormal oxidation occurred.[4,5] It was of interest to study the oxidation behavior of 1-aminopiperidines only monosubstituted at each α-carbon atom with electron-withdrawing groups to determine the course of the reaction, to relate the results to proposed reaction schemes, and to determine if ring closure in these instances also occurs stereospecifically.[6b,d]

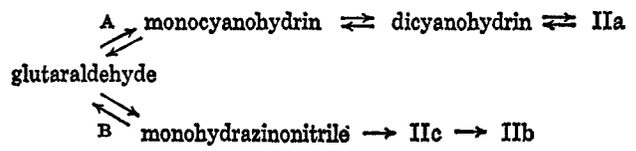
Results and Discussion

The known[9,10] 1-amino-2,6-dicyanopiperidine (IIa) was conveniently prepared by the cyclization of glutaraldehyde and dicyanohydrin *via* a Strecker-type reaction with hydrazine (Scheme II). The reaction proved to be complex, and the nature of the products was influenced by the solvents used. In water, the reaction of glutaraldehyde and dicyanohydrin, prepared *in situ*, with hydrazine at 0–10° resulted in a very rapid formation of an insoluble solid, reported[9] to be 1-amino-2-carboxamido-6-cyanopiperidine (IIc). When allowed to continue at 25° for 4 days, the reaction yielded 1-amino-2,6-dicarboxamidopiperidine (IIb) in 68% yield. The reaction of the dicyanohydrin with hydrazine in aqueous ethanol at room temperature yielded crude 1-amino-2,6-dicyanopiperidine (IIa) in about 20% yield from which the pure material was obtained in about 8% yield by crystallization from ethanol followed by chloroform–dibutyl ether mixture. The same result was obtained when the dicyanohydrin was prepared *in situ*. Contrary to the report of Johnson and Crosby,[9] the dicyano derivative was not formed when 100% ethanol was used as solvent. In the rapid formation of IIc in the aqueous system, there was no evidence for the initial formation of IIa. This suggested that the formation of these products occurred by two different routes. This is not unreasonable, since nitriles are not usually hydrolyzed so rapidly by weak base at low temperatures. The existence of two simultaneous reaction sequences (Scheme III) might explain the observed results. The initial steps of sequence A are strongly base catalyzed. The equilibria in this sequence are not favored and the formation of by-products *via* sequence B or a similar path becomes competing or even predominating. The driving force of sequence B appears to be the rapid formation of insoluble product IIc, shifting all equilibria in this direction and accounting for the high yield of IIb without the prior formation of the corresponding dicyano compound IIa. Stewart

SCHEME II



SCHEME III



(1) This is the 44th in a series of papers concerned with the preparation and decomposition of azo compounds. For the previous paper in this series, see C. G. Overberger and J.-P. Anselme, *J. Am. Chem. Soc.*, **86**, 658 (1964).

(2) This paper comprises a portion of the dissertation submitted by S. Altscher in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Polytechnic Institute of Brooklyn.

(3) C. G. Overberger, L. C. Palmer, B. S. Marks, and N. R. Byrd, *J. Am. Chem. Soc.*, **77**, 4100 (1955).

(4) C. G. Overberger, P.-T. Huang, and T. B. Gibb, *ibid.*, **75**, 2082 (1953).

(5) C. G. Overberger, G. Kesslin, and P.-T. Huang, *ibid.*, **81**, 3779 (1959).

(6) (a) C. G. Overberger and B. S. Marks, *ibid.*, **77**, 4104 (1955); (b) C. G. Overberger, J. G. Lombardino, and R. G. Hiskey, *ibid.*, **79**, 6430 (1957); (c) C. G. Overberger and L. P. Herin, *J. Org. Chem.*, **27**, 417, 2423 (1962); (d) C. G. Overberger, J. G. Lombardino, and R. G. Hiskey, *J. Am. Chem. Soc.*, **80**, 3009 (1958); (e) C. G. Overberger, N. P. Marullo, and R. G. Hiskey, *ibid.*, **83**, 1374 (1961); (f) C. G. Overberger and N. P. Marullo, *ibid.*, **83**, 1378 (1961).

(7) J. Kenner and E. C. Knight, *Ber.*, **69**, 341 (1936).

(8) (a) W. R. McBride and H. W. Kruse, *J. Am. Chem. Soc.*, **79**, 572 (1957); (b) W. H. Urry, H. W. Kruse, and W. R. McBride, *ibid.*, **79**, 6568 (1957); (c) W. R. McBride and E. M. Bens, *ibid.*, **81**, 5546 (1959).

(9) H. E. Johnson and D. G. Crosby, *J. Org. Chem.*, **27**, 1298 (1962).

(10) Private communication from Dr. D. T. Cameron of the Charles Pfizer Co.

and Li[11] have demonstrated the existence of a series of similar rapid equilibria in the formation of α-aminonitriles from cyanohydrins and amines.[12] The rapid formation of a well-characterized benzal derivative established the structure as the 1,1-disubstituted hydrazine rather than the isomeric 3,7-dicarboxamidohomopiperidazine.

Careful examination of the various crystallization fractions of this hydrazine and of the remaining reaction mixture failed to indicate the presence of a second stereoisomer. Since only one isomer was obtained, it became important to know its configuration. Both infrared and nmr studies failed to yield useful information (see Experimental Section). However, the *trans* configuration for IIb is suggested both by the analysis of its oxidation products and by its method of preparation.

Structure of IIa was similarly established. Elemental analysis confirmed the formula $C_7H_{10}N_4$. Infrared analysis showed the sharp NH stretching and bending absorption bands expected of this structure. The hydrazine formed a well-characterized benzal derivative, confirming its structure as the 1,1-disubstituted hydrazine. The nmr spectrum showed a broad band of 6 protons at τ 8.05 and a single peak of two protons at τ 6.29, assigned tentatively to the amino protons. A doublet corresponding to two protons was observed at τ 6.08 (J = 10.8 cps), assigned to the two α-hydrogens. Careful examination suggested that higher resolution would show two doublets or a quartet. This would be expected if the ring were restricted to one chair conformation, most probably the diequatorial *cis*-2,6-dicyano-substituted one.

Oxidation of 1-amino-2,6-dicarboxamidopiperidine (IIb) with mercuric oxide proceeded very readily in aqueous ethanol at 62°, giving a quantitative elimination of nitrogen in 1 hr. Only two diamides were isolated from the reaction mixture in a combined yield of 99+%. Separation by crystallization yielded *trans*-cyclopentane-1,2-dicarboxamide and 1-pentene-1,5-dicarboxamide in 34 and 66% yields, respectively. Careful infrared analysis of the products failed to indicate the presence of *cis*-cyclopentane-1,2-dicarboxamide. It is estimated that the *cis* compound, if present, would amount to less than 5% of the total. The 1-pentene-1,5-dicarboxamide, a new compound, was further characterized by quantitative hydrogenation with uptake of 1 mole of hydrogen to form pimelic diamide. Assignment of the double bond to the α,β position was confirmed by its ultraviolet absorption spectrum, λ_{max} 217 mμ (ε 12,400), identical with the data reported for crotonamide.[13]

Oxidation of 1-amino-2,6-dicyanopiperidine (IIa) proceeded in a more complicated fashion, and was influenced by both solvent and oxidant. Bromine in ethanol[4,5] led to a very rapid reaction at 0–10°, yielding only 60% of theoretical nitrogen, 20% of a high-melting (235–237°) solid, and a liquid. The elemental analysis and the molecular weight of the difficultly soluble solid suggested the tetrazene structure resulting from the normal oxidation. The infrared spectrum indicated retention of the piperidine ring and the ultraviolet absorption maximum at λ_{max} 269 mμ (ε 8520) corresponded with the data reported for tetraalkyltetrazenes.[3a,14]

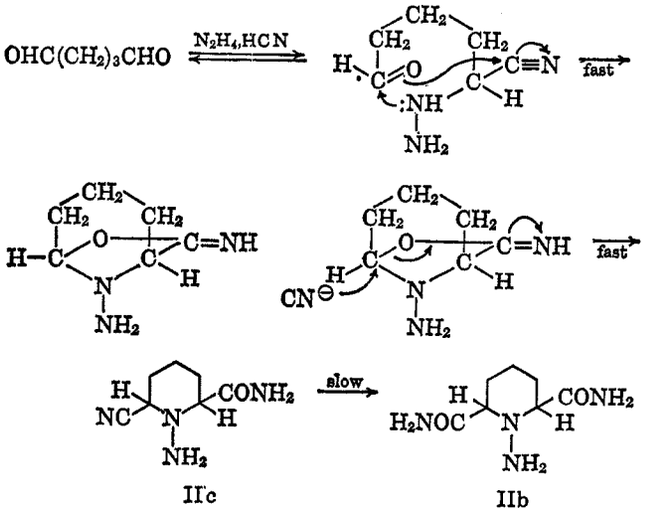
Infrared analysis of the liquid portion showed considerable nitrile hydrolysis to ester and amide groups. Separation and identification was attempted by hydrolysis, followed by esterification and gas chromatographic analysis of the methyl esters. No volatile products were obtained, suggesting that the liquid portion consisted of higher molecular weight, nonvolatile products. These may have been formed by reactions involving the reactive α hydrogens or *via* resonance-stabilized free radicals. Identical results were obtained when the oxidation was carried out with potassium permanganate in acetone.[3]

With mercuric oxide in ethanol,[6] no reaction was observed at 60°, starting material being recovered unchanged. The use of butanol as solvent[15] at 117° resulted in reduction of mercuric oxide. Less than half of the theoretical amount of nitrogen was evolved. Hydrolysis of the liquid reaction product followed by esterification gave no volatile products. Oxidation in aqueous ethanol at 62° gave incipient reaction in 24 hr. A further change in the reaction medium to water–dimethyl sulfoxide (1:2) resulted in a rapid, abnormal oxidation. The nitrogen collected was 92% of theory. No solid tetrazene was found. Hydrolysis of the concentrated reaction mixture, followed by esterification and analysis by gas chromatographic procedure, showed the presence of 12.3% of *cis*-coupled, 24.8% of *trans*-coupled, and 8.4% of the linear, unsaturated products as the corresponding methyl esters. The ratio of cyclized:linear olefinic products was 4.4:1.

Mechanism.—Collapse of the stable nitrene intermediate by the abnormal process may proceed *via* an open ion pair or a biradical. For reasons formerly stated[4-6a] there is some reason to believe that considerable contribution to the nitrene is made by the biradical form.

(11) T. D. Stewart and C. Li, *J. Am. Chem. Soc.*, **60**, 2782 (1938).

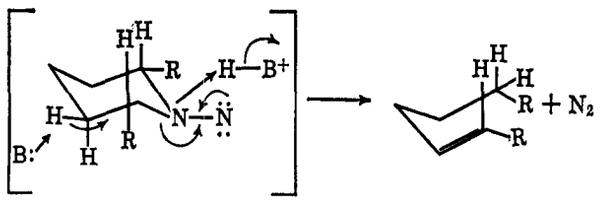
(12) The presence of the monohydrazinonitrile of glutaraldehyde is not unreasonable in this instance. As shown in the following reaction sequence, the intramolecular concerted cyclization could rapidly yield the intermediate bicyclic compound followed by a rapid SN2 attack by cyanide ion to yield IIc. Compound IIb is then formed by the expected slow hydrolysis of the nitrile group under the reaction conditions shown. Chemical and spectral evidence supported structure IIb for this compound (see Experimental Section).



(13) C. A. Grob and B. Fischer, *Helv. Chim. Acta*, **38**, 1796 (1955).

(14) W. E. Bull, J. A. Eaton, and L. F. Audrieth, *J. Am. Chem. Soc.*, **80**, 2516 (1958).

(15) R. L. Hinman and K. L. Hamm, *ibid.*, **81**, 3294 (1959).



The radical path is the most likely process for formation of the unsaturated, linear products by a disproportionation reaction. Their formation *via* the previously suggested E2-type of elimination[5,6] appears a much less likely mechanism. If operative to any appreciable extent, product formation in the presence of the nucleophilic dimethyl sulfoxide should be strongly directed toward olefin formation rather than cyclization, contrary to the observed results.

It is further suggested that the direction of nitrene collapse is governed largely by steric considerations. Formation of cyclized products appears energetically preferred, except where the bulk of the substituents presents steric hindrance to cyclization; then the processes leading to olefin formation become energetically more important and competitive with cyclization. When R = $CONH_2$, olefin formation predominates over cyclization by about 2:1, but, when R = CN, cyclization is favored to olefin formation by 4:1. Cyclization to form the cyclopentane-1,2-dicarboxamide must overcome steric crowding due to the bulky amide groups. In the dicyano-substituted nitrene, steric crowding is reduced, thereby favoring cyclization.

Conclusions regarding the stereospecific ring closure cannot be definite due to the absence of data resulting from the reaction of *cis* and *trans* isomers of the same compound. Isolation of only the *trans*-coupled product from the oxidation of 1-amino-2,6-dicarboxamidopiperidine, which is probably the *trans* isomer, suggests that ring closure is also stereospecific when electronegative substituents are present. The *trans*:*cis* ratio of coupled products obtained from the oxidation of the dicyano substituted hydrazine is of little value in this consideration, since the hydrolytic conditions presumably isomerize the mixture toward enrichment in the more stable *trans* isomer.

Experimental Section[16]

Preparation of Glutaraldehyde Solution.—Commercially available 25% aqueous solutions from Shell Chemical Co. or Union Carbide Chemical Co. were used without purification when fresh. Older materials were frequently discolored and gave nonreproducible results. Preparation of fresh samples for use as needed by the following procedure was preferred.

A mixture of 128 g (1.0 mole) of redistilled 2-ethoxy-3,4-dihydro-2H-pyran, 200 ml of water, and 3 g of concentrated hydrochloric acid was stirred under nitrogen for 2 hr at 35–40°. A clear solution was formed after 0.5 hr. After neutralization of the reaction mixture with 16 g of 10% sodium carbonate solution, sufficient water was added to give 400 g of solution containing 25% by weight of glutaraldehyde.

1-Amino-2,6-dicarboxamidopiperidine (IIb).—Following the procedure of Johnson and Crosby,[9] the product melting at 240–244° was prepared in 63% yield. Recrystallization from water raised the melting point to 249–250°. An analytical sample melted at 252–254° (lit.[9] mp 246–250°).

Anal. Calcd for $C_7H_{14}N_4O_2$: C, 45.18; H, 7.58; N, 30.08. Found: C, 45.07; H, 7.60; N, 30.10.

Benzal derivative (from 25% ethanol) melted at 222.0–223.2°.

Anal. Calcd for $C_{14}H_{18}N_4O_2$: C, 61.30; H, 6.62; N, 20.45. Found: C, 61.39; H, 6.74; N, 20.38.

The infrared spectrum of IIb (KBr pellet) showed very strong amide bands. No nitrile absorptions were observed. NH stretching and bending bands could not be observed due to the strong overlap from the more intense amide absorptions. The nmr spectrum (determined in deuterium oxide solution using 3-trimethylsilylpropane-1-sodium sulfonate as internal standard) exhibited a broad multiplet corresponding to eight protons at τ 8.15 and a triplet corresponding to two protons at 6.02 ($J_{AB} = J_{BX} = 5.5$ cps). The doublet normally associated with this A_2X system[17] presumably was part of the multiplet. No bands corresponding to the amide protons were observed.

A search for a second isomer of IIb proved unsuccessful. Examination of the crystallization filtrates disclosed only additional IIb and a small amount of lower melting solid (230–232°). Its infrared spectrum was very similar to that of the pure IIb with the exception of the appearance of very weak nitrile absorptions, suggesting the presence of some IIc.

1-Amino-2,6-dicyanopiperidine (IIa) was prepared by a modified procedure of Johnson and Crosby.[9] To a solution of 32.6 g (0.5 mole) of potassium cyanide in 55 ml of water was added with cooling 50 g (0.23 mole) of 50% sulfuric acid. The resulting slurry was added with cooling to 100 ml (0.25 mole) of a 25% solution of glutaraldehyde in water. The mixture was stirred at 10–15° for 2 hr and filtered to yield a yellow solution of glutaraldehyde and dicyanohydrin. A solution of 14.7 g (0.25 mole) of 85% hydrazine hydrate in 65 ml of ethanol was added to the dicyanohydrin solution and stirred at 30° for 24 hr. The mixture was evaporated to dryness *in vacuo* while the temperature was maintained below 30°. The residue was extracted with 1 l. of boiling ether in small portions. Concentration of this extract at 15° to about 100 ml gave a solid. Two recrystallizations from ethanol followed by a slow crystallization from chloroform–dibutyl ether mixture yielded 6.1 g (8.1%) of white crystals, mp 101–102°. An analytical sample melted at 103.5–104.5°.

Anal. Calcd for $C_7H_{10}N_4$: C, 56.00; H, 6.71; N, 37.35. Found: C, 56.30; H, 6.86; N, 37.13.

Benzal derivative (from ethyl acetate–ethanol), white platelets, melted at 188.5–189.5°.

Anal. Calcd for $C_{14}H_{14}N_4$: C, 70.60; H, 5.93; N, 23.51. Found: C, 70.59; H, 6.10; N, 23.29.

The infrared spectrum of IIa (KBr pellet) exhibited absorption bands at 3.0 and 3.1 (NH stretch), 6.27 (strong, NH bending), and 4.48 μ (medium C≡N). The nmr spectrum in deuteriochloroform, using TMS as internal standard, showed a multiplet of 6 protons at τ 8.05, a single peak at 6.29 tentatively assigned to the two amino hydrogens, and a doublet at 6.08 ($J = 10.8$ cps) assigned to the two tertiary hydrogens.

Oxidation of 1-Amino-2,6-dicarboxamidopiperidine (IIb) with Mercuric Oxide.—To a solution of 1.86 g (0.01 mole) of IIb in 135 ml of 65% ethanol heated to 62° were added portionwise 4.35 g (0.02 mole) of yellow mercuric oxide. One-third of the mercuric oxide was added and nitrogen evolution was observed within 1 min. After 10 min the suspended solids had turned dark green and a second portion of mercuric oxide was added. The third portion was similarly added after another 15 min. The nitrogen evolved was collected at a steady rate, and was complete after 47 min (248 ml, 99 ± 1%). The cooled solution was filtered through Supercel and the filter cake was extracted with three 40-ml portions of boiling water. The combined extracts and filtrates were kept in the refrigerator for 72 hr. A white solid was obtained weighing 0.41 g and melting at 300–305°. Concentration of the filtrate to dryness gave 1.16 g of off-white solid melting at 155–160°. The total yield of solid products was 1.57 g, a quantitative recovery.

The higher melting product was *trans*-cyclopentane-1,2-dicarboxamide. Its infrared spectrum was identical with that of an authentic sample[18] and a mixture melting point was not depressed. No other product was found in this fraction.

(16) Melting points are corrected. Elemental analyses were by Alfred Bernhardt Mikroanalytisches Laboratorium, Mülheim (Ruhr), Germany, and Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Infrared Spectra were obtained on a Perkin-Elmer Model 21 infrared spectrophotometer. Ultraviolet spectra were obtained on a Beckman Model DK-2 spectrophotometer. Nmr spectra were taken on a Varian HR-60 instrument operating at 60 Mc at 25°.

(17) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1963, pp 77–81.

(18) G. O. Aspinall and W. Baker, *J. Chem. Soc.*, 743 (1950).

The lower melting solid was further fractionated by refluxing with 35 ml of methanol and filtering the hot solution from insoluble solid (0.26 g, mp 150–300°). The infrared analysis of the insoluble solid showed the presence only of *trans*-cyclopentane-1,2-dicarboxamide and 1-pentene-1,5-dicarboxamide. They were estimated to be present in about equal amounts by the absorptions at 7.94 and 8.75 μ characteristic for the *trans*-diamide and at 8.25 μ characteristic for the unsaturated diamide.

From the methanol solution, 0.81 g of 1-pentene-1,5-dicarboxamide was obtained. Its infrared spectrum was identical with that of an authentic sample (see below) and a mixture melting point was not depressed. Summary of the results indicated that of the 1.57 g of solid oxidation product obtained, 34% was *trans*-cyclopentane-1,2-dicarboxamide and 66% was 1-pentene-1,5-dicarboxamide.

Assignment of the 1-pentene-1,5-dicarboxamide structure to the lower melting product was confirmed by the following. (a) One mole of hydrogen was absorbed per mole of product to yield pimelic diamide. A solution of 0.475 g (0.00305 mole) of the lower melting fraction in 40 ml of methanol, catalyzed by a prereduced suspension of 0.1 g of platinum oxide in 10 ml of methanol, absorbed 72.0 ± 0.5 ml of hydrogen at atmospheric pressure at 27°, corresponding to a 96.0 ± 0.7% yield. From the mixture, 0.455 g of white solid were separated. Recrystallized from methanol it melted at 173.7–174.5°. The mixture melting point with an authentic sample of pimelic diamide was not depressed. (b) Location of the double bond in the α,β position was demonstrated by the near identity of the ultraviolet absorption spectrum with that reported for crotonamide.[12] Observed absorptions at 218 and 240 μ gave log ϵ 4.09 and 3.19, respectively, compared with log ϵ 4.2 and 3.2 reported for crotonamide.

1-Pentene-1,5-dicarboxylic Acid.—An adaptation of the procedure reported by Brown and Baker[19] was used. To a cooled solution of 32.3 g (0.31 mole) of malonic acid in 45 ml of pyridine was added 20.2 g (0.155 mole) of freshly distilled methyl 4-formylbutyrate.[20] After addition of 1 ml of piperidine, the mixture was allowed to stand for 3 days and then gently warmed on a water bath for 2 hr.[20] The mixture was poured into 400 ml of 5% hydrochloric acid and extracted with toluene, and the toluene solution in turn was extracted with sodium carbonate solution. Acidification of this solution yielded an oil which was extracted with benzene and dried, and the benzene was removed *in vacuo*. The residual crude monoester (12 g) was saponified by heating in a solution of 12.5 g of sodium hydroxide in 70 ml of water on a steam bath for 4 hr. The mixture was poured into ice and 28 ml of concentrated hydrochloric acid and 7.4 g (68%) of 1-pentene-1,5-dicarboxylic acid, mp 119–120°, was obtained. Recrystallization from water gave an analytical sample, mp 119.5–121.0°.

Anal. Calcd for $C_7H_{10}O_4$: C, 53.17; H, 6.38. Found: C, 53.30; H, 6.28.

***trans*-Cyclopentane-1,2-dicarboxamide.**—The infrared spectrum of this diamide[18] prepared from *trans*-cyclopentane-1,2-dicarboxylic acid[21a–c] showed typical strong amide absorptions and in addition, medium absorptions at 7.94 and 8.75 μ characteristic of this diamide.

***cis*-Cyclopentane-1,2-dicarboxamide.**—*cis*-Cyclopentane-1,2-dicarboxylic acid[21d] was refluxed with excess thionyl chloride on a steam bath for 1 hr. The excess thionyl chloride was removed *in vacuo* and the residue slowly was poured into concentrated ammonium hydroxide at −20°. The solution was concentrated to dryness. The solid formed was recrystallized from methanol to yield the *cis*-cyclopentane-1,2-dicarboxamide as a white solid, mp 141.0–141.7° (48% yield).

Anal. Calcd for $C_7H_{12}N_2O_2$: C, 53.80; H, 7.75; N, 17.39. Found: C, 53.55; H, 7.84; N, 17.58.

The infrared spectrum showed the typical strong amide absorptions. In addition, a strong amide II band appeared at 6.21 and a weak band at 12.8 μ both characteristic for this *cis*-diamide.

1-Pentene-1,5-dicarboxamide.—1-Pentene-1,5-dicarboxylic acid was refluxed with excess thionyl chloride on a steam bath for 1 hr. The excess thionyl chloride was removed *in vacuo* and the residue slowly was poured into concentrated ammonium hydroxide at −20°. A precipitate was formed, filtered, and recrystallized from methanol to yield 1-pentene-1,5-dicarboxamide (73%), mp 161.0–162.0°.

Anal. Calcd for $C_7H_{12}N_2O_2$: C, 53.80; H, 7.75; N, 17.93. Found: C, 53.92; H, 7.82; N, 18.00.

The infrared spectrum showed the typical strong amide absorptions. In addition, a medium absorption was observed at 8.25 μ, characteristic of this unsaturated diamide.

Oxidation Reactions of 1-Amino-2,6-dicyanopiperidine (IIa). With Bromine in Ethanol.—Following the general procedure of Overberger and co-workers,[4,5] 3.00 g (0.02 mole) of IIa was oxidized with 3.20 g (0.02 mole) of bromine in 100 ml of absolute ethanol at 0–6°. Nitrogen elimination ceased after about one-half of the theoretical quantity was collected. From the reaction mixture 0.650 g (21.6%) of an off-white solid, mp 230–235°, was recovered by filtration. After recrystallization from dimethyl sulfoxide, it melted at 235–237° with decomposition.

Anal. Calcd for $C_{14}H_{16}N_8$ (tetrazene): C, 56.76; H, 5.40; N, 37.83; mol wt, 296. Found: C, 57.00; H, 5.80; N, 37.10; mol wt, 310 (cryoscopic in dimethyl sulfoxide).

Infrared analysis (KBr pellet) showed no NH absorptions, a weak nitrile absorption at 4.4–4.5 μ, and absorptions at 8.80, 8.97, 9.13, and 9.27 μ indicative of a piperidine ring structure.

A yellow-orange, viscous liquid weighing 1.90 g was recovered from the filtrate of the tetrazene by extraction with chloroform after neutralization with base. It was hydrolyzed by standard and also by unusual procedures,[22,23] followed by esterification with diazomethane in ether. The products were then subjected to gas chromatographic analysis using a 10-ft polyethylene glycol succinate on Chromosorb W column at 180–190°. In none of these hydrolyses were any volatile products observed, except occasional trace quantities (<1%) of the dimethyl esters.

With Potassium Permanganate in Acetone.—Following the procedure of Overberger and co-workers[3] 1.66 g (0.11 mole) of IIa was oxidized. From the reaction mixture was recovered 0.33 g (19.9%) of the solid tetrazene, mp 230–235°, and 0.73 g of a yellow-orange liquid. Hydrolysis of the liquid followed by esterification gave no volatile methyl esters by gas chromatographic analysis.

With Mercuric Oxide in Ethanol at 60°.—No nitrogen liberation or color change of the reaction mixture were observed after 5 hr, unreacted IIa being recovered from the reaction mixture.

With Mercuric Oxide in 1-Butanol at 117°.—Following the procedure of Hinman and Hamm,[15] only partial (40%) nitrogen elimination was observed. A deep red liquid was isolated from the reaction which failed to yield any volatile products as determined by gas chromatographic analysis after hydrolysis and esterification.

With Mercuric Oxide in 65% Ethanol at 62°.—Nitrogen elimination was very slow and incomplete in 24 hr. Only a liquid product was obtained (68%) which, after hydrolysis and esterification, showed about 1% of each of the three expected diesters by gas chromatographic analysis. No other volatile products were observed.

With Mercuric Oxide in 65% Dimethyl Sulfoxide at 67°.—Nitrogen elimination proceeded very rapidly with each partial addition of mercuric oxide, the total reaction being completed in about 0.5 hr. Nitrogen yield was 92%. The hot reaction mixture was filtered through Supercel, and the filter cake was washed well with warm dimethyl sulfoxide. The combined washings and filtrate were concentrated at 70° (2 mm) using a 6-in. glass helix packed column, yielding a red, viscous liquid product. This contained some residual solvent. There was no evidence for the presence of the tetrazene. The liquid product was hydrolyzed by refluxing with 20 ml of 60% sulfuric acid and 0.5 g of sodium chloride for 3 hr at 160–165°. The cooled mixture was poured into 30 ml of water, filtered to remove a small amount of black solid, neutralized with 25% sodium hydroxide, and concentrated to dryness. The residue

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was extracted with methanol and the extract was esterified with excess diazomethane. From 5.7 mmoles of IIa there were obtained, by gas chromatographic analysis, 1.41 mmoles of *trans*-1,2-dicarbomethoxycyclopentane, 0.70 mmoles of *cis*-1,2-dicarbomethoxycyclopentane, and 0.48 mmole of 1,5-dicarbomethoxy-1-pentene. The total yield is 45.4%. Individual yields were 24.8% of the *trans*-coupled, 12.3% of the *cis*-coupled, and 8.4% of the unsaturated dimethyl esters.

The Cyclization of N-Chloro-4-alkylpiperidines[1]

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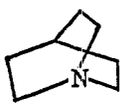
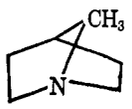
N-Chloro-4-ethylpiperidine and N-chloro-3-methyl-4-ethylpiperidine when cyclized by the Hofmann–Loeffler reaction gave a mixture of the respective quinuclidines and 1-azabicyclo[2.2.1]heptanes. N-Chloro-4-propylpiperidine in the same reaction gave 2-methylquinuclidine and N-chloro-4-methylpiperidine gave 1-azabicyclo[2.2.1]heptane. The N-chloroamines from 2-methyl- and 3-methylpiperidine gave no bicyclic amines.

The cyclization of N-halo-4-ethylpiperidines by the Hofmann–Loeffler reaction has been reported to yield quinuclidine (I) in one investigation[2] and 7-methyl-1-azabicyclo[2.2.1]heptane (II) in another study.[3]



I



II

In order to resolve these discrepancies the cyclization of N-chloro derivatives of 4-ethylpiperidine, 4-propylpiperidine, and 4-ethyl-3-methylpiperidine was reinvestigated and the products were examined by gas chromatography. In addition the study was extended to the cyclization of the N-chloro derivatives of the isomeric methylpiperidines. The amines formed were isolated as picrates and hydrochlorides. The yields of picrates and polymers isolated are given in Table I.

TABLE I

YIELDS OF PICRATES AND NONSTEAM VOLATILE MATERIALS IN CYCLIZATION OF N-CHLORO-4-ALKYLPIPERIDINES

Piperidine (g)	Temp, °C	Yield of picrates, g	Yield, %	Yield of nonsteam volatile material, g
4-Ethyl (10)	0	2.73	21.36	1.76
	20	2.41	18.66	1.93
	55	1.88	14.71	1.80
4-Methyl (20)	0–5	1.06	3.80	1.22
4-Propyl (10)	0–5	1.43	12.0	...
4-Ethyl-3-methyl (10)	0	2.78	21.58	...

The cyclizations in all cases except 2-methyl- and 3-methylpiperidines produced bicyclic nitrogen compounds. Mixtures of amines were formed in each cyclization and could be separated by gas chromatography on a column packed with base-washed Chromosorb P as a solid support and Tetronic 701 as the liquid phase using an ionization detector with a nitrogen–hydrogen mixture or argon as a carrier gas. The reaction products when present in large enough amounts were collected using a preparation size column. Separation of the products by ordinary fractional distillation was not successful.

Cyclization of N-chloro-4-ethylpiperidine at 0, 20, and 55° produced mixtures of quinuclidine (I) and 7-methyl-1-azabicyclo[2.2.1]heptane (II). Approximately equal amounts of the two compounds were formed at 0 and 55°. At the intermediate temperature of 20° the ratio of quinclidine (I) to 7-methyl-1-azabicyclo[2.2.1]heptane (II) was 60:40.

The quinuclidine (I) and 7-methyl-1-azabicyclo[2.2.1]heptane (II) were identified by comparison of their retention times and nmr spectra with samples prepared from 4-(2-hydroxyethyl)piperidine[4] and 4-(1-hydroxyethyl)piperidine, respectively. The mixture of picrates from these compounds upon repeated crystallizations from acetone–ligroin gave the pure quinuclidine derivative.

In the irradiation of N-chloro-4-ethylpiperidine at 0° a third component appeared upon analysis by gas chromatography in insufficient amounts to be characterized. The formation of this compound only at the lower temperature suggested that it was probably 3,4,5,6-tetrahydro-4-ethylpyridine.

Ring closure of N-chloro-4-ethyl-3-methylpiperidine at 0° produced 3-methylquinuclidine and 3,7-dimethyl-1-azabicyclo[2.2.1]heptane in equal amounts. The product with the smaller retention time was identified as 3,7-dimethyl-1-azabicyclo[2.2.1]heptane by its nmr spectrum. The compound, however, was obtained in amounts too small to be characterized. 3-Methylquinuclidine was identified by its nmr spectrum and by its picrate.[5]

The cyclization of N-chloro-4-propylpiperidine gave six products according to gas chromatographic analysis; only one was identified positively. The first peak which comprised 70% of the products was obtained pure by preparative gas chromatography and was identified by its nmr spectrum and picrate[6] as 2-methylquinuclidine.

The fifth component was the only product that could be separated in large enough amounts by preparative gas chromatography for spectral analysis. The infrared and nmr spectra indicated the presence of an imine (CH=N) group, and the nmr spectrum showed a methyl triplet. These data definitely rule out 7-

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