[CONTRIBUTION FROM THE DEPARTMENT OF PATHOLOGY, THE GEORGETOWN UNIVERSITY MEDICAL CENTER[1]]

SOME REACTIONS OF 4,7,8,9-TETRAHYDROISOINDOLINE AND PERHYDROISOINDOLE

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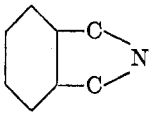
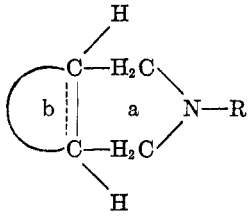
During the past several years we have conducted studies directed toward the preparation of derivatives of the basic isoindole nucleus (A) with various nitrogen and ring substituents, endo bridges, and states of ring hydrogenation. These compounds may also be looked upon as substituted pyrrolines or pyrrolidines having another ring fused at the 3,4 positions (B).



(A)



(B)

We have previously reported the preparation of several series of isoindole derivatives in which the nitrogen substituent is alkyl (1) and in which it is dialkylaminoalkyl (2). We have also employed the tertiary amine N-alkyl isoindoles in the preparation of several series of quaternary and bis-quaternary salts (3).

The isoindole type nucleus in some of these compounds has proved to have interesting pharmacological properties. Because the toxicity of the isoindole ring variations we have investigated was relatively low, it was considered of interest to incorporate this type of nucleus into other types of pharmacologically active compounds.

At this time we should like to report the preparation of the unsubstituted base 4,7,8,9-tetrahydroisoindoline. This base is a typical secondary amine and has been utilized in the scheme of reactions shown in Chart I.

The reduction of tetrahydrophthalimide (I) by means of lithium aluminum hydride proceeded smoothly to yield 4,7,8,9-tetrahydroisoindoline (II). The base (II), was converted to perhydroisoindole (III) by reduction with hydrogen over platinum oxide. The secondary amines, II and III, were converted into representative derivatives such as ureas and thioureas.

The base (II) on reaction with ethylene oxide in methanol gave β-(4,7,8,9-tetrahydroisoindolinyl)ethanol (IV), which on hydrogenation yielded the corresponding perhydroisoindolylethanol (V). The *p*-nitrobenzoate esters of these two alcohols, VI and VII, were obtained on reaction with *p*-nitrobenzoyl chloride.

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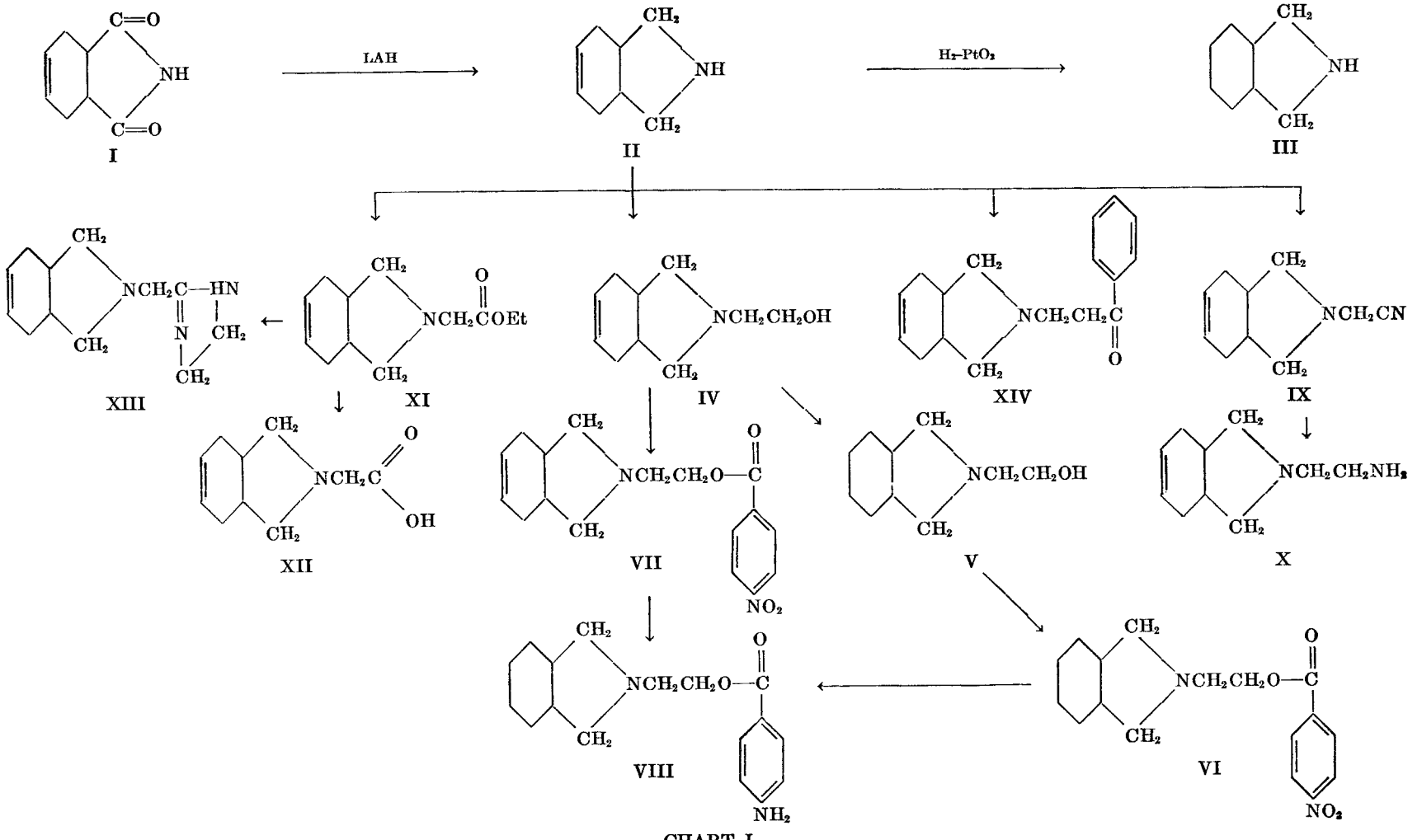
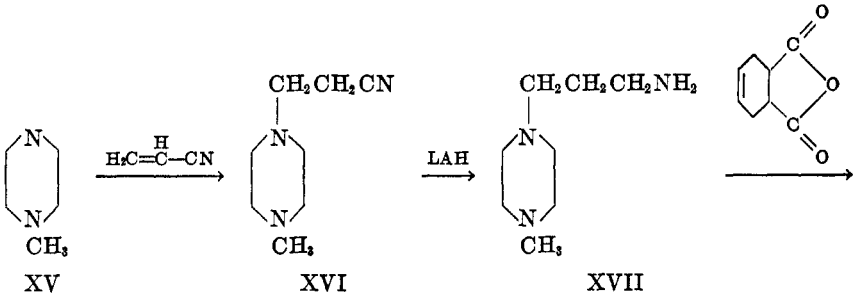
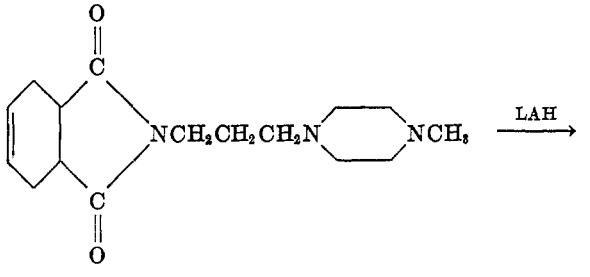

LAH
H₂-PtO₂
I
II
III
XIII
XI
IV
XIV
IX
XII
VII
V
X
VIII
VI
CHART I

The two esters, VI and VII, on reduction yielded the same *p*-aminobenzoate ester (VIII) as shown by mixture melting points and infrared spectra. The ester (VIII) has been synthesized by two independent routes.

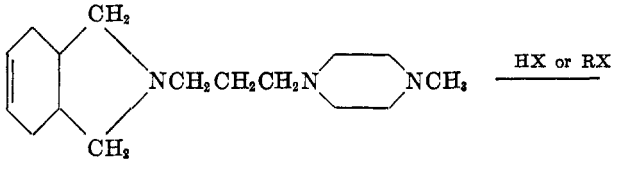
The reaction of the base (II) with chloroacetonitrile was studied and compound IX was obtained. When IX was reduced in the presence of lithium aluminum hydride, the corresponding *β*-(4,7,8,9-tetrahydroisoindolinyl)ethyl amine (X), was produced. This compound is isomeric with partially hydrogenated tryptamine.



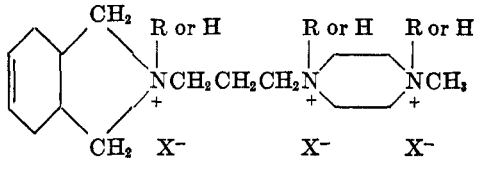
XV XVI XVII



XVIII



XIX



XX

CHART II

When ethyl chloroacetate was refluxed with a two-*molar* quantity of II, the ethyl 4,7,8,9-tetrahydroisoindolinylacetate (XI) was obtained. This ester, on careful saponification followed by neutralization, gave the corresponding

4,7,8,9-tetrahydroisoindolinyl acetic acid (XII). This amino acid is highly water-soluble and because of its relation to indoleacetic acid was tested as a plant growth regulator. The auxin activity of this substance was negative on the organisms tried. It also did not promote nor inhibit the growth of *B. aerogenes*.

The alcohol (V), readily reacted with diphenylacetyl chloride yielding the corresponding ester. The base (II), also readily underwent a Mannich type reaction with acetophenone yielding the isoindolinyl acetophenone derivative (XIV). The ester (XI), when reacted with ethylene diamine, gave an imidazole derivative (XIII).

Because of our interest in hypotensive agents and the good activity found in several of these series of bis-quaternary salts containing the isoindole type nuclei (2, 3), we prepared some tris-quaternary salts containing the isoindole type nucleus as one of the nitrogen bearing groups. One such series of tris-quaternary salts is illustrated in the reaction sequence of Chart II. N-Methylpiperazine (XV), was converted to N-methyl, N'-cyanoethyl piperazine (XVI), by reaction with acrylonitrile. Then this was reduced to the corresponding amine (XVII) with lithium aluminum hydride. This primary amine group then could be reacted with any of the anhydrides previously employed (2, 3) to yield the corresponding N-methyl, N'-phthalimidopropyl piperazines (XVIII). These imides on reduction yielded the desired tris-tertiary amine bases, as illustrated by N-methyl, N'-(γ-4,7,8,9-tetrahydroisoindolinylpropyl)piperazines (XIX) which then were converted to the desired tris-quaternary salts (XX).

EXPERIMENTAL

4,7,8,9-Tetrahydroisoindoline (II). A solution of 60 g. of lithium aluminum hydride in 1700 ml. of dry ether was prepared in a 3-liter, 3-necked, reaction flask fitted with a Soxhlet extractor and a Hershberg stirrer. The thimble of the extractor was charged with 150 g. of *cis*-Δ^4-tetrahydrophthalimide (I) which was transferred to the reaction flask by continuous extraction. After 24 hours the extraction and reaction were complete. The Soxhlet extractor then was replaced by a long condenser and the reaction mixture was cooled in an ice-bath. While stirring vigorously the reaction mixture was decomposed by the dropwise addition of water which was added at such a rate as to just maintain reflux. An excess of 35 ml. of water was added, the mixture was stirred an additional hour, and inorganic material was filtered off with suction. The inorganic precipitate was pressed well and washed with three portions of ether. After drying over sodium sulfate, the ether was stripped off and the residue was distilled *in vacuo* to yield 60 g. of base, b.p. 76–80°/15 mm. or 90–93°/26 mm., n_D^{20} 1.5110.

Anal. Calc'd for $C_8H_{13}N$: C, 77.99; H, 10.64; N, 13.37.
Found: C, 77.93; H, 10.70; N, 13.64.

Phenylthiourea derivative. This was prepared in the usual way and after recrystallization from alcohol melted at 164–165°.

Anal. Calc'd for $C_{15}H_{18}N_2S$: N, 10.84. Found: N, 10.98.

Naphthylurea derivative. This was prepared in the usual way and was recrystallized from alcohol, m.p. 216–217°.

Anal. Calc'd for $C_{19}H_{20}N_2O$: N, 9.58. Found: N, 9.51.

Phenylurea derivative. Prepared in the usual way, and recrystallized from alcohol, it had m.p. 152.5–153.5°.

Anal. Calc'd for $C_{15}H_{18}N_2O$: N, 11.56. Found: N, 11.66.

p-Bromophenylsulfonamide derivative. Prepared in the usual way, and recrystallized from alcohol, it had m.p. 102–103°.

Anal. Calc'd for $C_{14}H_{16}BrNO_2S$: N, 4.09. Found: N, 4.13.

Hydrochloride. Prepared from the base and alcoholic HCl in isopropyl alcohol and precipitated with ether, it had m.p. 131.5–132.5°.

Anal. Calc'd for $C_8H_{14}ClN$: Ionic Cl, 22.20. Found: Ionic Cl, 22.07.

Perhydroisoindole (III). A solution of 32 g. of 4,7,8,9-tetrahydroisoindoline in 300 ml. of methanol was reduced with hydrogen over 0.5 g. of platinum oxide catalyst at room temperature. The absorption of hydrogen was rapid and the theoretical amount was absorbed in one hour. The solution was filtered and the excess methanol was stripped off. The base foamed very badly on several attempted distillations and was not further purified. It was converted into the following derivatives.

Hydrochloride. This was prepared in isopropyl alcohol with alcoholic HCl and was precipitated with dry ether, m.p. 123.5–125°.

Anal. Calc'd for $C_8H_{16}ClN$: C, 59.43; H, 9.98; N, 8.66; Ionic Cl, 21.94.
Found: C, 59.55; H, 10.00; N, 8.83; Ionic Cl, 22.11.

The *picrate* was prepared in the usual way and was recrystallized from methanol, m.p. 162–163°.

Anal. Calc'd for $C_{14}H_{18}N_4O_7$: N, 15.81. Found: N, 15.93.

The *phenylthiourea derivative* was prepared in the usual manner and was recrystallized from alcohol, m.p. 176–178°.

Anal. Calc'd for $C_{15}H_{20}N_2S$: N, 10.76. Found: N, 11.10.

Phenylurea. This derivative was prepared in the usual manner and was recrystallized from alcohol, m.p. 133–135°.

Anal. Calc'd for $C_{15}H_{20}N_2O$: N, 11.47. Found: N, 11.52.

Naphthylurea. This derivative was prepared in the usual manner and was recrystallized from alcohol, m.p. 182–183.5°.

Anal. Calc'd for $C_{19}H_{22}N_2O$: N, 9.52. Found: N, 9.60.

N-(Cyanomethyl)-4,7,8,9-tetrahydroisoindoline (IX). A mixture of 17.7 g. (0.143 mole) of the base II and 5.4 g. (0.0715 mole) of chloroacetonitrile was refluxed for 4 hours in 100 ml. of toluene. The mixture was cooled in the refrigerator and the crystalline hydrochloride of the base II was filtered off. On recrystallization from methanol and washing with ether it melted at 132–133°. The filtrate with the ether washings was stripped of all solvent and the remaining oil was distilled *in vacuo*. After two distillations there was obtained 8 g., 69%, of material boiling at 80°/0.4 mm. or 67°/0.2 mm., n_D^{20} 1.5031.

Anal. Calc'd for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27.
Found: C, 74.14; H, 8.60; N, 17.41.

N-(β-Aminoethyl)-4,7,8,9-tetrahydroisoindoline (X). Lithium aluminum hydride (2 g.) was dissolved in 400 ml. of anhydrous ether in a 1-liter, 3-necked, reaction flask equipped with a stirrer, dropping-funnel, and reflux condenser with drying tube. A solution of 6 g. of the nitrile (IX) in 100 ml. of ether was added dropwise with stirring. When addition of the nitrile had been completed the mixture was refluxed with stirring for 2 hours. Then the mixture was cooled and decomposed by the dropwise addition of water added so as to just maintain reflux of the ether; and then a 5-ml. excess was added. The inorganic material was filtered off, pressed tightly, washed three times with ether, and the ether extracts and washings were combined, dried over sodium sulfate, and the ether stripped off. The residual oily liquid was distilled *in vacuo* yielding 6.1 g., b.p. 97–101°/3.5 mm., n_D^{20} 1.5067.

Anal. Calc'd for $C_{10}H_{18}N_2$: C, 72.24; H, 10.91; N, 16.85.
Found: C, 72.14; H, 11.05; N, 17.14.

The *dihydrochloride* was prepared from the amine with alcoholic hydrogen chloride in isopropyl alcohol. It was recrystallized best from isopropyl alcohol to which a few drops of alcoholic HCl had been added. The material formed rectangular plates, m.p. 180–180.5°.

Anal. Calc'd for $C_{10}H_{20}Cl_2N_2$: Ionic Cl, 29.64. Found: Ionic Cl, 29.68.

Phenyl β-4,7,8,9-tetrahydroisoindolinylethyl ketone hydrochloride (XIV). The base II was subjected to the Mannich reaction with acetophenone in essentially the same procedure described in Organic Reactions (4), except that after the reaction period was completed the

mixture was diluted with acetone and the hydrochloride salt was precipitated with ether. When employing 0.1-*molar* quantities the Mannich base hydrochloride was obtained in 60% yield and after two recrystallizations from alcohol-ether it melted at 153–155°.

Anal. Calc'd for $C_{17}H_{22}ClNO$: C, 69.94; H, 7.60; N, 4.80; Ionic Cl, 12.15.
Found: C, 70.16; H, 7.56; N, 4.68; Ionic Cl, 12.16.

N-(β-Hydroxyethyl)-4,7,8,9-tetrahydroisoindoline (IV). The base II, 25.5 g. (0.20 mole) was dissolved in 500 ml. of methanol and cooled in an ice-bath. Ethylene oxide was slowly bubbled into the cold solution until the weight had increased by 8.4–8.8 g. (0.19–0.20 mole). The flask then was tightly stoppered and allowed to come to room temperature. After standing overnight, the methanol was distilled off and the product was distilled *in vacuo* to yield 21 g., 63%, of material b.p. 85–90°/1.0 mm.

Anal. Calc'd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38.
Found: C, 71.95; H, 9.87; N, 8.25.

N-(β-Hydroxyethyl)perhydroisoindole (V). Compound IV (7 g.) dissolved in 100 ml. of methanol was hydrogenated at room temperature over a 5% palladium-on-charcoal catalyst. Absorption was rapid and the theoretical quantity of hydrogen was absorbed in less than an hour. The solution was filtered and the methanol was removed by distillation. The product, 5.5 g., was obtained as a colorless liquid, b.p. 78–82°/0.75 mm.

Anal. Calc'd for $C_{10}H_{19}NO$: C, 70.96; H, 11.32; N, 8.28.
Found: C, 70.75: H, 11.25; N, 8.05.

β-(4,7,8,9-Tetrahydroisoindolinyl)ethyl p-nitrobenzoate hydrochloride (VII). To 5.01 g. (0.03 mole) of the amino alcohol (IV) dissolved in 45 ml. of benzene was added 5.57 g. (0.03 mole) of *p*-nitrobenzoyl chloride dissolved in 45 ml. of benzene. The mixture was refluxed for 2 hours. An oil separated. On cooling the reaction mixture, the oil solidified and was collected by filtration. The product after 2 recrystallizations from alcohol-ether melted at 157–158° and weighed slightly over 10 g. (nearly quantitative yield).

Anal. Calc'd for $C_{17}H_{21}ClN_2O_4$: C, 57.87; H, 6.00; N, 7.94; Ionic Cl, 10.05.
Found: C, 58.01; H, 6.00; N, 7.99; Ionic Cl, 10.05.

β-(Perhydroisoindolyl)ethyl p-nitrobenzoate hydrochloride (VI). This ester was prepared in the same manner as the preceeding ester, VII, from the corresponding amino alcohol, V. It likewise was obtained in almost quantitative yield, m.p. 171.5–172.5°.

Anal. Calc'd for $C_{17}H_{23}ClN_2O_4$: C, 57.54; H, 6.53; N, 7.90; Ionic Cl, 9.99.
Found: C, 57.78; H, 6.77; N, 7.89; Ionic Cl, 10.21.

β-(Perhydroisoindolyl)ethyl p-aminobenzoate monohydrochloride (VIII). *Method A.* A solution of 5.0 g. of compound VII dissolved in 400 ml. of methanol was reduced over a 5% palladium-on-charcoal catalyst at room temperature. Absorption was rapid and stopped when the theoretical amount of hydrogen had been consumed. The solution was filtered, concentrated to about 100 ml., and stored overnight in the refrigerator. The crystalline material that separated was filtered off and had m.p. of 229–231° which was not changed on recrystallization.

Method B. The compound prepared by method *A* above was likewise obtained on reduction of compound VI and it had a melting point of 229–231°. When equal quantities of the materials prepared in methods *A* and *B* were mixed, the mixture melted at 229–231°.

Anal. Calc'd for $C_{17}H_{25}ClN_2O_2$: C, 62.85; H, 7.76; N, 8.62; Ionic Cl, 10.92.
Found: C, 62.99; H, 7.90; N, 8.38; Ionic Cl, 10.80.

Ethyl (4,7,8,9-tetrahydroisoindolinyl)acetate (XI). A solution of 32.03 g. (0.26 mole) of 4,7,8,9-tetrahydroisoindoline in 150 ml. of toluene was refluxed with 15.9 g. (0.13 mole) of ethyl chloroacetate for 4 hours. The mixture was cooled and placed in the refrigerator overnight. The crystals of 4,7,8,9-tetrahydroisoindoline hydrochloride that separated were filtered off and washed with ether. The toluene solution and ether washings were combined, washed twice with water, and dried over sodium sulfate. After filtering the solvent was stripped off and the residual oil was fractionated *in vacuo*. A yield of 21 g. of product with b.p. 73–75°/0.2 mm. was obtained.

Anal. Calc'd for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69.
Found: C, 68.83; H, 9.15; N, 6.86.

4,7,8,9-Tetrahydroisoindolinylacetic acid (XII). To a solution of 10.5 g. of the preceeding compound, XI, dissolved in 40 ml. of absolute ethanol was added the saponification equivalent of an alcoholic (0.5 *N*) solution of KOH. After standing in a closed system for 3 days, an amount of alcoholic HCl equivalent to the KOH was added. The KCl was filtered off and the filtrate was evaporated to dryness under reduced pressure. The dried residue was extracted with anhydrous acetone and concentrated to a small volume. On adding ether to the acetone concentrate and refrigerating the solution the acid separated. This crude product softened at 120° and melted at 138–139°. Several recrystallizations from anhydrous ethyl acetate raised the melting point to 146–147°. In spite of precautions in using solvents of low water content, the acid crystallized as the monohydrate.

Anal. Calc'd for $C_{10}H_{15}NO_2 \cdot 1\ H_2O$: C, 60.28; H, 8.60; N, 6.87.

Found: C, 60.35; H, 8.49; N, 7.03.

N-(2-Imidazolemethyl)-4,7,8,9-tetrahydroisoindoline dihydrochloride (XIII). A mixture of 10.5 g. of ethyl α-(4,7,8,9-tetrahydroisoindolinyl)acetate (XI) and 50 ml. of 95–100% ethylene diamine was refluxed for 8 hours. The excess ethylene diamine was stripped off under reduced pressure, the residue distilled at 0.5 mm., and the portion boiling 173–179° collected. This product solidified in the receiver. The distillate was dissolved in alcohol and treated with alcoholic HCl. Ether precipitated the dihydrochloride which after recrystallization from acetone-ether-alcohol mixture melted at 176.5–178.5°. The material thus obtained was a monohydrate.

Anal. Calc'd for $C_{12}H_{21}Cl_2N_3 \cdot 1H_2O$: C, 48.63; H, 7.14; N, 14.18; Ionic Cl, 23.93.

Found: C, 48.61, H, 7.36; N, 14.33; Ionic Cl, 23.66.

β-(Perhydroisoindolyl)ethyl diphenylacetate hydrochloride. To 8.5 g. (0.05 mole) of N-(β-hydroxyethyl)perhydroisoindole dissolved in 50 ml. of benzene was added 11.5 g. (0.05 mole) of diphenylacetyl chloride. The mixture was let stand overnight and then was refluxed 2 hours. When cool the benzene solution was extracted with 10% hydrochloric acid The acid extract was made basic and extracted with several portions of ether. This procedure was repeated twice more. The final extract was dried over sodium sulfate and filtered. After removing the ether, the base was dissolved in alcohol and treated with alcoholic HCl. Ether precipitated the hydrochloride salt as an oil which on refrigeration and repeated slurrying with anhydrous ether finally crystallized after 2 months. The crude hydrochloride melted at 116–119°. Recrystallization from anhydrous ethyl acetate gave the salt with m.p. 129–130°.

Anal. Calc'd for $C_{24}H_{30}ClNO_2$: C, 72.07; H, 7.56; N, 3.50.

Found: C, 72.21; H, 7.47; N, 3.71.

N-Methyl, N'-(cyanoethyl)piperazine (XVI). N-Methylpiperazine (XV), 50.08 g. (0.5 mole), dissolved in 150 ml. of benzene was placed in the usual apparatus. Stirring was started and a solution of 26.55 g. (0.5 mole) of acrylonitrile in an equal volume of benzene was added dropwise. When all acrylonitrile had been added, the mixture was refluxed several hours and allowed to stand overnight. The benzene was stripped off and the residue distilled *in vacuo*. There was obtained 61 g., 79.5%, of material with b.p. 68–72°/0.3 mm., n_D^{20} 1.4744.

Anal. Calc'd for $C_8H_{15}N_3$: C, 62.71; H, 9.86; N, 27.43.

Found: C, 62.57; H, 9.66; N, 27.58.

N-Methyl, N'-(γ-aminopropyl)piperazine (XVII). An ether solution of the preceding cyano compound, XVI, was reduced with lithium aluminum hydride in the usual way. From 58 g. of the cyano compound only 23 g. of the corresponding amine was obtained, a relatively poor yield. The amine boiled at 52°/0.3 mm.

N-(γ-Tetrahydrophthalimido)propyl, N'-methylpiperazine (XVIII). To 20.0 g. (0.13 mole) of *cis*-Δ^4-tetrahydrophthalic anhydride was added 22 g. (0.14 mole) of N-methyl, N'-(γ-aminopropyl)piperazine without solvent. After the exothermic reaction had subsided the mixture was warmed gently until homogeneous and then was heated up to 170–190° where it was maintained for 2 hours. The imide was isolated by vacuum distillation and there was obtained 33 g. of product b.p. 160–165°/0.2 mm.

Dihydrochloride of the imide (XVIII). A portion of the base dissolved in isopropyl alcohol

was treated with an excess of alcoholic HCl and the dihydrochloride was precipitated by adding ether and cooling. It melted at 255–258° dec. Recrystallization from methanol gave the dihydrochloride with m.p. 258–259° dec.

Anal. Calc'd for $C_{16}H_{27}Cl_2N_3O_2$: C, 52.75; H, 7.47; N, 11.53; Ionic Cl, 19.47.
Found: C, 52.84; H, 7.77; N, 11.26; Ionic Cl, 19.41.

2-[N-methyl, N'-(γ-piperazinopropyl)]-4,7,8,9-tetrahydroisoindoline (XIX). A solution of 15 g. of lithium aluminum hydride was prepared in 1 liter of anhydrous ether in the usual apparatus (2-liter). A solution of 30 g. of the imide (XVIII) in ether was slowly added at such a rate as to just maintain reflux of the ether. The mixture was stirred vigorously for several hours and then was decomposed by the drop-wise addition of water and a slight excess of water was added. Inorganic salts were filtered off, pressed well, and washed several times with ether. The filtrate and washings were combined and dried over sodium sulfate. The ether was stripped off and the residual base was distilled *in vacuo*. The fraction b.p. 136–142°/0.1 mm. was collected.

Anal. Calc'd for $C_{16}H_{29}N_3$: C, 72.95; H, 11.10; N, 15.95.
Found: C, 72.90; H, 10.88; N, 16.21.

Trihydrochloride of XIX. The trihydrochloride of XIX was prepared in the usual way and was recrystallized from isopropyl alcohol, m.p. 270–271° dec.

Anal. Calc'd for $C_{16}H_{32}Cl_3N_3$: Ionic Cl, 28.53. Found: Ionic Cl, 28.54.

The tris-quaternary methonium salt of XIX (XX). The trimethiodide of base XIX was readily obtained by treating the base dissolved in absolute methanol with an excess of methyl iodide. The crude material melted at 213–215°. Recrystallization from methanol or isopropyl alcohol raised the melting point to 217–218°.

Anal. Calc'd for $C_{19}H_{38}I_3N_3$: Ionic I, 55.24. Found: Ionic I, 54.94.

SUMMARY

The synthesis of the heterocyclic secondary amine bases 4,7,8,9-tetrahydroisoindoline and perhydroisoindole is described. These bases have been characterized and several derivatives of each have been prepared. The bases have been employed as the heterocyclic group in the preparation of heterocyclic alkanols, alkyl amines, nitriles, and alkyl carboxylic acids. The bases underwent a typical Mannich reaction. Tris-quaternary salts have been prepared in which the isoindole type nucleus is one of the nitrogen-bearing rings.

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