[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

The Synthesis of 4-Methyl-1,4-diazabicyclo[5.4.0]undecane and Its 6-Phenyl Derivative

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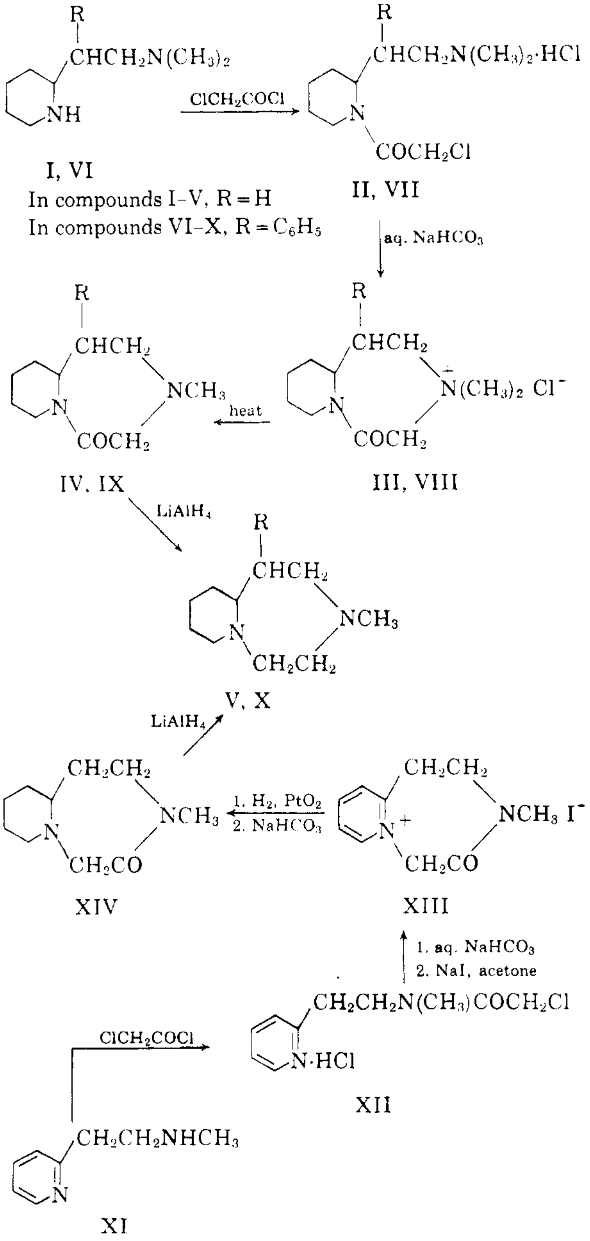
4-Methyl-1,4-diazabicyclo[5.4.0]undecane was synthesized from 2-vinylpyridine by two procedures. The 6-phenyl derivative was prepared from 2-benzylpyridine.

2-Vinylpyridine reacted with dimethylamine hydrochloride to yield 2-(2-dimethylaminoethyl)-pyridine monohydrochloride.[3] The dihydrochloride[4] was hydrogenated, catalytically, whereby 2-(2-dimethylaminoethyl)piperidine dihydrochloride was obtained. The base of this substance[5] (I) was treated with chloroacetyl chloride to obtain 1-chloroacetyl-2-(2-dimethylaminoethyl)piperidine hydrochloride (II). When sodium bicarbonate was added to an aqueous solution of II at room temperature, the liberated base cyclized rapidly to form 2-keto-4-methyl-1,4-diazabicyclo[5.4.0]undecane methochloride (III). When heated, the quaternary base (III) was converted into the tertiary base 2-keto-4-methyl-1,4-diazabicyclo[5.4.0]undecane (IV). Reduction of IV with lithium aluminum hydride yielded 4-methyl-1,4-diazabicyclo[5.4.0]-undecane (V), which was obtained also by the following series of reactions. Interaction of 2-vinylpyridine with methylamine hydrochloride produced, after the addition of alkali, 2-(2-methylaminoethyl)pyridine[6] (XI) which reacted with chloroacetyl chloride to yield 2-[2-(*N*-methyl-*N*-chloroacetylamino)ethyl]pyridine hydrochloride (XII). An acetone solution of the base of XII was treated with sodium iodide whereupon the corresponding iodoacetylamino compound was formed; it cyclized immediately to 3-keto-4-methyl-1,4-diazabicyclo[5.4.0]undeca-1(7),8,10-trienium iodide (XIII), which precipitated from the solution. Hydrogenation of XIII in the presence of platinum dioxide yielded 3-keto-4-methyl-1,4-diazabicyclo-[5.4.0]undecane (XIV). Treatment of XIV with lithium aluminum hydride converted it into V.



The structure of XII was proved by its conversion into XVI in the following manner. Compound XII was hydrogenated in the presence of platinum dioxide. The base of the product obtained, 2-[2-(*N*-methyl-*N*-acetylamino)ethyl]piperidine (XV), was reduced with lithium aluminum hydride to 2-[2-(methylethylamino)ethyl]piperidine which was converted into the dihydrochloride (XVI). The structure of XVI was established by its synthesis from 2-vinylpyridine. This substance reacted

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[1] Abstracted from the Ph.D. dissertation of J. L. Hughes, University of Michigan, 1961.

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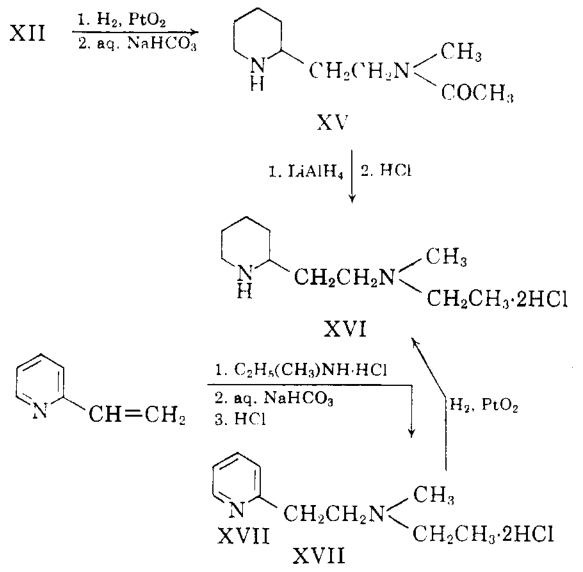
[3] H. E. Reich and R. Levine, *J. Am. Chem. Soc.*, **77**, 4913 (1955).

[4] T. Morikawa, *J. Pharm. Soc. Japan*, **75**, 593 (1955); *Chem. Abstr.*, **50**, 5656 (1956).

[5] H. L. Cohen and L. M. Minsk, *J. Am. Chem. Soc.*, **79**, 1759 (1957).

[6] H. E. Reich and R. Levine, *J. Am. Chem. Soc.*, **77**, 5434 (1955).



with methylethylamine hydrochloride to form 2-[2-(methylethylamino)ethyl]pyridine hydrochloride which was converted into the base and then into the dihydrochloride (XVII). This product (XVII) was hydrogenated with the use of platinum dioxide to form XVI.

Compounds VII–X, analogous to II–V, were prepared from 2-(1-phenyl-2-dimethylaminoethyl)-piperidine (VI) which was obtained in the following manner. Interaction of 2-benzylpyridine, paraformaldehyde and dimethylamine hydrochloride yielded 2-(1-phenyl-2-dimethylaminoethyl)pyridine monohydrochloride which was converted into the dihydrochloride.[7] This salt was hydrogenated catalytically with the formation of a mixture of the dihydrochlorides of racemates (VIa and VIb) of 2-(1-phenyl-2-dimethylaminoethyl)piperidine. After separation of the dihydrochlorides, VIa and VIb, and conversion of the salts into the bases, the latter compounds were transformed into Xa and Xb, respectively, by the stepwise procedures used to obtain V from I. During the formation of VIIa, a portion of this substance cyclized to VIIIa.

EXPERIMENTAL

2-(2-Dimethylaminoethyl)pyridine. A mixture of 105 g. (1.0 mole) of 2-vinylpyridine, 164 g. (2.0 moles) of dimethylamine hydrochloride, and 150 ml. of water was stirred and refluxed for 5 hr. After extraction with ether the aqueous layer, which contained 2-(dimethylaminoethyl)pyridine monohydrochloride, was made strongly alkaline with sodium hydroxide and then filtered. The product was removed from the filtrate by extraction with ether and the use of a continuous liquid extractor.[8] The extract was dried over sodium hydroxide, the solvent was removed and the residue distilled; b.p. 51–53°/0.1 mm. (lit.,[4] b.p. 86–87°/7.5 mm.); yield, 120 g. (80%).

The dihydrochloride, prepared in ether, was recrystallized from absolute ethanol; m.p. 195–197° (lit.,[4] m.p. 178°).

Anal. Calcd. for $C_9H_{16}N_2Cl_2$: C, 48.44; H, 7.23; N, 12.55; Cl, 31.78. Found: C, 48.41; H, 7.33; N, 12.81; Cl, 31.98.

The dipicrate, prepared in ethanol, was recrystallized from acetone; m.p. 179–181° (lit.,[4] m.p. 181–182°).

2-(2-Dimethylaminoethyl)piperidine (I). A mixture of 30 g. of 2-(2-dimethylaminoethyl)pyridine, 34 ml. of concd. hydrochloric acid, 100 ml. of ethanol, and 0.75 g. of platinum dioxide was hydrogenated, under an initial pressure of 48 lbs., for 2 hr. After filtration and removal of the solvents, the residue was made basic and the product was distilled; b.p. 45–47°/0.1 mm. (lit.,[5] b.p. 80–81°/9 mm.).

The dihydrochloride, prepared in ether, melted at 244–246° after recrystallization from absolute ethanol.

Anal. Calcd. for $C_9H_{22}Cl_2$: C, 47.16; H, 9.68; N, 12.22; Cl, 30.94. Found: C, 47.15; H, 9.63; N, 12.20; Cl, 30.77.

1-Chloroacetyl-2-(2-dimethylaminoethyl)piperidine hydrochloride (II). A solution of 12.0 g. of chloroacetyl chloride in 75 ml. of chloroform was cooled and stirred while 15.6 g. of I, dissolved in 75 ml. of chloroform, was added, dropwise. The mixture was stirred for 12 hr. at room temperature, the solvent was removed and the residue was recrystallized from ethanol; m.p. 177–179°; yield, 22.0 g. (82%).

Anal. Calcd. for $C_{11}H_{22}ON_2Cl_2$: C, 49.07; H, 8.24; N, 10.41. Found: C, 49.27; H, 8.44; N, 10.16.

2-Keto-4-methyl-1,4-diazabicyclo[5.4.0]undecane methochloride (III). Sodium bicarbonate (8.4 g.) was added, in portions, to a stirred solution of 20.0 g. of II in 75 ml. of water. The mixture was stirred for 1 hr., the solvent was removed and the residue was extracted with 350 ml. of hot chloroform. The filtered extract was cooled to 0° and the precipitate was recrystallized from chloroform; m.p. 215° dec.; yield, 16.0 g. (90%).

Anal. Calcd. for $C_{11}H_{21}ON_2Cl$: C, 56.76; H, 9.10; N, 12.04; Cl, 15.23. Found: C, 56.52; H, 9.31; N, 12.05; Cl, 15.44.

2-Keto-4-methyl-1,4-diazabicyclo[5.4.0]undecane (IV). Compound III (24.0 g.) was heated in a distillation flask with a semimicro burner under a pressure of 50 mm. until a clear liquid was obtained. The pressure was then reduced to 0.3 mm. and IV was distilled; b.p. 104–108°/0.3 mm.; yield 11.0 g. In order to remove traces of III carried over in the distillation, the crude distillate was dissolved in ether, the solution was filtered, the solvent was removed from the filtrate and the residue was distilled; b.p. 106–108°/0.3 mm.; yield, 9.0 g. (48%).

Anal. Calcd. for $C_{10}H_{18}ON_2$: C, 65.89; H, 9.96; N, 15.37. Found: C, 65.83; H, 9.99; N, 15.11.

The picrate, prepared in ethanol, was recrystallized from acetone; m.p. 207–211°.

Anal. Calcd. for $C_{16}H_{21}O_8N_5$: C, 46.71; H, 5.15. Found: C, 46.91; H, 5.23.

The chloroaurate, prepared in 5% hydrochloric acid, was recrystallized from absolute ethanol; m.p. 153–156°.

Anal. Calcd. for $C_{10}H_{18}ON_2 \cdot HAuCl_4$: C, 23.00; H, 3.67; Au, 37.76. Found: C, 23.14; H, 3.68; Au, 37.65.

4-Methyl-1,4-diazabicyclo[5.4.0]undecane (V) *from* IV *and from* XIV. (a) Compound IV (6.0 g.), dissolved in 200 ml. of ether, was added to a stirred mixture of 3.1 g. of lithium aluminum hydride and 250 ml. of ether. The mixture was stirred for 18 hr., cooled, 9 ml. of water added, dropwise, and the mixture was stirred for 24 hr. After filtration, the filtrate was dried over anhydrous magnesium sulfate and the solvent was removed. Because of excessive foaming, the residue could not be distilled. It was dissolved in ether and the solution was treated with hydrogen chloride. The precipitated dihydrochloride was recrystallized from methanol-ether; m.p. 260–265° dec.; yield, 4.9 g. (62%).

Anal. Calcd. for $C_{10}H_{22}N_2Cl_2$: C, 49.79; H, 9.20; N, 11.61; Cl, 29.40. Found: C, 49.82; H, 9.22; N, 11.38; Cl, 29.26.

The dipicrate, prepared in ethanol, was recrystallized from ethanol; m.p. 210° dec.

Anal. Calcd. for $C_{22}H_{26}O_{14}N_8$: C, 42.17; H, 4.19. Found: C, 42.31; H, 4.21.

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[7] British Pat. **589,625** (1947); *Chem. Abstr.*, **42**, 226 (1948). U. S. Pat. **2,508,332** (1950); *Chem. Abstr.*, **44**, 7352 (1950).

[8] A. I. Vogel, *Practical Organic Chemistry*, Longmans, Green and Co., New York, Third Ed., 1956, p. 152.

(b) Compound XIV (5.7 g.), described below, was reduced with 3.1 g. of lithium aluminum hydride in the manner mentioned above. The crude product was converted into the dihydrochloride; m.p. and mixed m.p. 260–265° dec.; yield, 5.5 g. (74%).

The dipicrate melted at 210° dec.; mixed m.p. 210° dec.

2-(1-Phenyl-2-dimethylaminoethyl)pyridine dihydrochloride. A mixture of 85 g. of 2-benzylpyridine, 21 g. of paraformaldehyde, 45 g. of dimethylamine hydrochloride, and 125 ml. of water was stirred and heated on a steam bath for 24 hr. The mixture was cooled and extracted with ether to remove unchanged 2-benzylpyridine. The aqueous solution was made strongly basic with 40% sodium hydroxide solution. The precipitated oily base was extracted with ether and the dried extract was treated with hydrogen chloride; the precipitated dihydrochloride was recrystallized from methanol; m.p. 190–191° (lit.,[7] m.p. 190°); yield, 104 g. (70%).

2-(1-Phenyl-2-dimethylaminoethyl)piperidine (VIa and VIb). A mixture of 30 g. of 2-(1-phenyl-2-dimethylaminoethyl)pyridine dihydrochloride, 150 ml. of methanol, 10 ml. of water, and 0.75 g. of platinum dioxide was hydrogenated under an initial pressure of 50 lb. for 2 hr. After filtration and removal of the solvent from the filtrate, the residue was dissolved in 150 ml. of hot methanol, and 30 ml. of ether was added. After the solution had been cooled at 0° for 16 hr., the precipitated dihydrochloride of VIa was removed by filtration and the filtrate (A) was retained. The salt was recrystallized several times from methanol; m.p. 300–303° dec.; yield, 12.2 g. (40%).

Anal. Calcd. for $C_{15}H_{26}N_2Cl_2$: C, 59.01; H, 8.58; N, 9.18; Cl, 23.23. Found: C, 58.88; H, 8.53; N, 9.43; Cl, 23.28.

The dihydrochloride was dissolved in water and the solution was made strongly basic with 40% sodium hydroxide solution. The base (VIa) was extracted with ether and after removal of the solvent from the dried extract, the residue was distilled; b.p. 123–126°/1 mm.

Anal. Calcd. for $C_{15}H_{24}N_2$: C, 77.52; H, 10.41; N, 12.06. Found: C, 77.45; H, 10.39; N, 12.08.

Filtrate A was evaporated to one half of its original volume, 100 ml. of ether was added, and the solution was maintained at 0° for 24 hr. The precipitate, the dihydrochloride of VIb, was filtered and recrystallized several times from absolute ethanol; m.p. 246–248° dec.; yield 11.3 g. (37%).

Anal. Calcd. for $C_{15}H_{26}N_2Cl_2$: C, 59.01; H, 8.58; N, 9.18; Cl, 23.23. Found: C, 59.04; H, 8.60; N, 9.43; Cl, 23.39.

A mixture of the dihydrochlorides of VIa and VIb melted at 247–252° dec.

The base VIb boiled at 105–108°/0.3 mm.

Anal. Calcd. for $C_{15}H_{24}N_2$: C, 77.52; H, 10.41; N, 12.06. Found: C, 77.38; H, 10.25; N, 11.85.

1-Chloroacetyl-2-(1-phenyl-2-dimethylaminoethyl)piperidine hydrochloride (VIIa *and* VIIb). A solution of 12.0 g. of chloroacetyl chloride in 75 ml. of chloroform was cooled and stirred while 23.2 g. of VIa in 75 ml. of chloroform was added, dropwise. After the mixture had been stirred for 12 hr. at room temperature the precipitate, a mixture of the dihydrochloride of VIa and VIIIa, was filtered. The filtrate (A) was retained. The precipitate was dissolved in 150 ml. of hot methanol, 60 ml. of ether was added and the solution was cooled. The material which precipitated, the dihydrochloride of VIa, was filtered and the filtrate (B) was retained. The precipitate weighed 9.5 g. after recrystallization from methanol; m.p. and mixed m.p. 300–303° dec.

After evaporation of filtrate A to dryness, the residue (VIIa) was recrystallized from ethanol-ether; m.p. 191–193° dec.; yield, 12.7 g. (37%).

Anal. Calcd. for $C_{17}H_{26}ON_2Cl_2$: C, 59.13; H, 7.59; N, 8.11. Found: C, 59.42; H, 7.76; N, 8.29.

After evaporation of filtrate B to dryness, the residue (VIIIa) was recrystallized from ethanol-ether; m.p. 223–225° dec.; yield, 7.1 g. (23%). The mixed m.p. with VIIIa, obtained in a separate experiment from VIIa, was 223–225° dec.

Chloroacetyl chloride (12.0 g.) and VIb (23.2 g.) were allowed to react in the manner described above. After the mixture had been stirred for 12 hr., the solvent was removed. Since the viscous residue (35 g., VIIb) could not be crystallized, it was used in the crude state for the preparation of VIIIb.

2-Keto-4-methyl-6-phenyl-1,4-diazabicyclo[5.4.0]undecane methochloride (VIIIa *and* VIIIb). Compound VIIa (7.0 g.) was converted into the base and cyclized according to the procedure used for the cyclization of II. The product (VIIIa) was isolated in the same manner as III. The yield of VIIIa was 6.0 g. (95%); m.p. 223–225° dec. after recrystallization from ethanol-ether.

Anal. Calcd. for $C_{17}H_{25}ON_2Cl$: C, 66.11; H, 8.16; N, 9.07; Cl, 11.48. Found: C, 65.86; H, 8.42; N, 8.87; Cl, 11.34.

In order to prepare VIIIb, the crude VIIb (35.0 g.) was converted into the base which was cyclized in the same manner as II. The aqueous solution of VIIIb was extracted with petroleum ether (b.p. 60–75°) to remove traces of VIb. After removal of the solvent from the aqueous solution, the product (VIIIb) was obtained from the residue by extraction with hot chloroform. The filtered extract was evaporated to dryness and the residue was recrystallized from a mixture of one part of chloroform and two parts of acetone; m.p. 220–222° dec.; yield, 17.3 g. (56%). A mixture of VIIIa and VIIIb melted at 218–220° dec.

Anal. Calcd. for $C_{17}H_{25}ON_2Cl$: C, 66.11; H, 8.16; N, 9.07; Cl, 11.48. Found: C, 65.85; H, 7.96; N, 8.81; Cl, 11.40.

2-Keto-4-methyl-6-phenyl-1,4-diazabicyclo[5.4.0]undecane (IXa *and* IXb). Compound VIIIa (22.0 g.) was converted into IXa by the procedure given for the preparation of IV; b.p. 158–162°/0.1 mm.; yield, 12.0 g. (64%).

Anal. Calcd. for $C_{16}H_{22}ON_2$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.24; H, 8.56; N, 10.59.

The chloroaurate, prepared in 5% hydrochloric acid, was recrystallized from absolute ethanol; m.p. 175–177° dec.

Anal. Calcd. for $C_{16}H_{22}ON_2 \cdot HAuCl_4$: C, 32.11; H, 3.87; N, 4.68; Au, 32.96. Found: C, 32.15; H, 3.81; N, 4.62; Au, 32.78.

Compound VIIIb (18.0 g.) was converted into IXb by the procedure given for the preparation of IV. The crude distillate, b.p. 170–175°/0.3 mm., after solidification, was recrystallized from 50% aqueous methanol; m.p. 114–116°; yield, 12.2 g. (81%).

Anal. Calcd. for $C_{16}H_{22}ON_2$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.25; H, 8.38; N, 11.07.

The chloroaurate, prepared in 5% hydrochloric acid, was recrystallized from absolute ethanol; m.p. 181–184° dec. A mixture of the chloroaurates of IXb and IXa melted at 174–177° dec.

Anal. Calcd. for $C_{16}H_{22}ON_2 \cdot HAuCl$: C, 32.11; H, 3.87; N, 4.68; Au, 32.96. Found: C, 32.16; H, 3.84; N, 4.73; Au, 33.20.

4-Methyl-6-phenyl-1,4-diazabicyclo[5.4.0]undecane (Xa *and* Xb). Compound IXa (7.1 g.) was reduced with 2.9 g. of lithium aluminum hydride by the procedure given for the preparation of V. The crude product (Xa), obtained from the reaction mixture after filtration and removal of the solvent, was distilled; b.p. 123–125°/0.3 mm.; yield, 5.5 g. (82%). The distillate solidified; m.p. 56–58°.

Anal. Calcd. for $C_{16}H_{24}N_2$: C, 78.63; H, 9.90; N, 11.46. Found: C, 78.44; H, 9.66; N, 11.27.

The dihydrochloride, prepared in ether, was recrystallized from absolute ethanol; m.p. 269–272° dec.

Anal. Calcd. for $C_{16}H_{26}N_2Cl_2$: C, 60.56; H, 8.26; N, 8.83; Cl, 22.35. Found: C, 60.64; H, 8.20; N, 8.90; Cl, 22.10.

Compound IXb (8.0 g.) was reduced with 3.2 g. of lithium aluminum hydride by the procedure used to prepare V. The crude product (Xb), obtained after filtration and removal of the solvent from the reaction mixture, solidified and was recrystallized from 80% aqueous methanol; m.p. 106–108°; yield, 6.8 g. (90%). A mixture of Xa and Xb melted at 59–61°.

Anal. Calcd. for $C_{16}H_{24}N_2$: C, 78.63; H, 9.90; N, 11.46. Found: C, 78.70; H, 9.80; N, 11.37.

The dihydrochloride of Xb, prepared in ether, was recrystallized from absolute ethanol; m.p. 278–280° dec. A mixture of this dihydrochloride with the dihydrochloride of Xa melted at 259–261°.

Anal. Calcd. for $C_{16}H_{26}N_2Cl_2$: C, 60.56; H, 8.26; N, 8.83. Found: C, 60.56; H, 8.34; N, 8.72.

2-(2-Methylaminoethyl)pyridine (XI). This compound was prepared from 105 g. of 2-vinylpyridine, 135 g. of methylamine hydrochloride and 150 ml. of water in the same general manner as 2-(2-dimethylaminoethyl)pyridine; m.p. 115–116°/27 mm. (lit.,[6] b.p. 117–118°/25 mm.); yield 101 g. (73%). The dipicrate, prepared in ethanol, was recrystallized from acetone; m.p. 193–196° (lit.,[6] m.p. 193.8–195.2°).

2-[2-(N-Methyl-N-chloroacetylamino)ethyl]pyridine hydrochloride (XII). Compound XII was prepared from 13.6 g. of XI and 12.0 g. of chloroacetyl chloride in the same manner as II. The solvent was removed from the reaction mixture and the residue was recrystallized from absolute ethanol; m.p. 143–147°; yield 21.0 g. (84%).

Anal. Calcd. for $C_{10}H_{14}ON_2Cl_2$: C, 48.21; H, 5.66; N, 11.25. Found: C, 48.16; H, 5.66; N, 11.05.

3-Keto-4-methyl-1,4-diazabicyclo[5.4.0]undeca-1(7)-8,10-trienium iodide (XIII). Compound XII (10.0 g.) was dissolved in water and converted into the base by the addition of sodium bicarbonate. The aqueous mixture was extracted with ether. The extract was dried, the solvent was removed and the residue was dissolved in 25 ml. of acetone. After the addition of 6.0 g. of sodium iodide, dissolved in 30 ml. of acetone, the mixture was stirred and refluxed for 1 hr. It was cooled, the precipitated mixture of XIII and sodium chloride was filtered, and the product was extracted with 150 ml. of boiling nitromethane. After filtration of the hot extract, the filtrate was cooled whereupon XIII precipitated; m.p. 210–212° dec. after recrystallization from nitromethane; yield 7.2 g. (67%).

Anal. Calcd. for $C_{10}H_{13}ON_2I$: C, 39.49; H, 4.31; N, 9.21; I, 41.73. Found: C, 39.58; H, 4.40; N, 9.25; I, 41.51.

3-Keto-4-methyl-1,4-diazabicyclo[5.4.0]undecane (XIV). Compound XIII (6.0 g.), dissolved in a mixture of 20 ml. of water and 50 ml. of ethanol, was hydrogenated in the presence of 0.5 g. of platinum dioxide under an initial pressure of 50 lb. for 1 hr. After filtration and removal of solvents from the filtrate, the residue was dissolved in water and sodium bicarbonate was added. The mixture was extracted with chloroform, the solvent was removed from the dried extract and the residue was distilled; b.p. 119–122°/1 mm.; m.p. 38–40°; yield 3.0 g. (82%).

Anal. Calcd. for $C_{10}H_{18}ON_2$: C, 65.89; H, 9.96; N, 15.37. Found: C, 65.91; H, 9.76; N, 15.20.

The hydrochloride, prepared in ether, was recrystallized from ethanol-ether; m.p. 220–222°.

Anal. Calcd. for $C_{10}H_{19}ON_2Cl$: C, 54.90; H, 8.70; N, 12.81; Cl, 16.21. Found: C, 54.83; H, 8.81; N, 13.01; Cl, 16.14.

The picrate, prepared in ethanol, was recrystallized from ethanol; m.p. 158–161°. A mixture of the picrates of IV and XIV melted at 145–149°.

Anal. Calcd. for $C_{16}H_{21}O_8N_5$: C, 46.71; H, 5.15. Found: C, 46.76; H, 5.21.

2-[2-(N-Methyl-N-acetylamino)ethyl]piperidine (XV). A mixture of 17.4 g. of XII, 75 ml. of ethanol, 10 ml. of water, and 0.75 g. of platinum dioxide was hydrogenated under an initial pressure of 60 lb. for 24 hr. After filtration and removal of the solvents from the filtrate, the residue was dissolved in 50 ml. of absolute ethanol, and a solution of sodium methoxide, prepared from 20 ml. of absolute methanol and 3.3 g. of sodium, was added. After 30 min., 75 ml. of benzene was added and the precipitated sodium chloride was removed by filtration through a sintered glass funnel. The solvents were removed from the filtrate and the residue was distilled; b.p. 112–113°/0.7 mm.; yield 8.0 g. (43%).

Anal. Calcd. for $C_{10}H_{20}ON_2$: C, 65.17; H, 10.94; N, 15.20. Found: C, 64.21; H, 10.90; N, 15.10.

The picrate, prepared in ethanol, was recrystallized from absolute ethanol; m.p. 160–162°.

Anal. Calcd. for $C_{16}H_{23}O_8N_5$: C, 46.49; H, 5.61; N, 16.94. Found: C, 46.46; H, 5.57; N, 16.34.

2-[2-(Methylethylamino)ethyl]piperidine dihydrochloride (XVI) (*from* XV *and from* XVII). (a) Compound XV (6.0 g.) was reduced with 3.1 g. of lithium aluminum hydride by the process used to prepare V. The crude product, obtained after filtration and evaporation of the solvent from the reaction mixture, was dissolved in ether and converted into the dihydrochloride (XVI) by the use of hydrogen chloride. After recrystallization from absolute ethanol, the salt melted at 234–237°; yield, 5.9 g. (76%).

Anal. Calcd. for $C_{10}H_{24}N_2Cl_2$: C, 49.38; H, 9.95; N, 11.52; Cl, 29.15. Found: C, 49.08; H, 9.66; N, 11.50; Cl, 29.35.

The dipicrate, prepared in ethanol, was recrystallized from absolute ethanol; m.p. 101–105°.

Anal. Calcd. for $C_{22}H_{28}O_{14}N_8$: C, 42.04; H, 4.49. Found: C 42.02; H, 4.74.

(b) A mixture of 14.0 g. of XVII, 90 ml. of ethanol, 10 ml. of water, and 0.5 g. of platinum dioxide was hydrogenated under an initial pressure of 52 lb. for 45 min. The residue (XVI), obtained after filtration and removal of the solvents, was recrystallized from absolute ethanol; m.p. 235–238° dec.; yield, 12.0 g. (84%). A mixture of the product with XVI, prepared from XV, melted at 235–238° dec.

The dipicrate, prepared in ethanol, was recrystallized from absolute ethanol; m.p. 101–105°. A mixture of this dipicrate with the dipicrate prepared from XVI, obtained from XV, melted at 101–105°.

2-[2-(Methylethylamino)ethyl]pyridine dihydrochloride (XVII). A mixture of 20.0 g. of 2-vinylpyridine, 21.0 g. of methylethylamine hydrochloride, and 35 ml. of water was stirred and refluxed for 4 hr. After extraction with ether, the aqueous layer was made basic with 40% sodium hydroxide solution. The product was extracted with ether and the dried extract was treated with hydrogen chloride; the precipitated dihydrochloride melted at 178–179° after recrystallization from absolute ethanol; yield 28.0 g. (65%).

Anal. Calcd. for $C_{10}H_{18}N_2Cl_2$: C, 50.64; H, 7.65; N, 11.81; Cl, 29.90. Found: C, 50.64; H, 7.66; N, 11.92; Cl, 29.74.

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