

Georgetown University Medical Center and Wyeth Laboratories

Spiranes. V (1). A Synthetic Route to Symmetrical and Unsymmetrical 3,9-Diazaspiro[5.5]undecanes

Leonard M. Rice, Charles H. Grogan, and Meier E. Freed

The synthesis of derivatives of the hitherto unreported 3,9-diazaspiro[5.5]undecane has been accomplished. Starting from the dianhydride of methanetetraacetic acid or from *N*-methyl-4-piperidone, synthetic paths have been developed which permit the preparation of either symmetrical or unsymmetrical derivatives.

The preparation of a number of heterocyclic spiranes has recently been reported (2). As a continuation of this work we would now like to report the synthesis of symmetrical and unsymmetrical derivatives of 3,9-diazaspiro[5.5]undecane (Ia). The synthesis of this spiro system was accomplished by two routes (Chart I). In route A, the dianhydride of methanetetraacetic acid (II), which was prepared by the method of Ingold and Nickolls (3), was treated with aqueous methylamine and the resulting amic acid was dehydrated by heating to 260° to obtain 3,9-dimethyl-3,9-diazaspiro[5.5]undecane-2,4,8,10-tetrone (IIIa). Lithium aluminum hydride reduction of this diimide led to 3,9-dimethyl-3,9-diazaspiro[5.5]undecane (Ib). In the alternate route (B, Chart I), 1-methylpiperidine-4,4-diacetic acid (4) (IVa) was prepared from 1-methylpiperidin-4-one and ethyl cyanoacetate in alcoholic ammonia, followed by hydrolysis of the imide with aqueous hydrochloric acid. The diester IVb had been obtained by McElvain and Lyle by esterification of the crude hydrolysate with ethanol and sulfuric acid. In our hands this procedure was found to be unsuited to the preparation of the diester on a larger scale. However, by prolonged refluxing of a solution of 1-methylpiperidine-4,4-diacetic acid hydrochloride in ethanol saturated with dry hydrogen chloride, IVb was prepared in yields of over 50% in 100 g. quantities. A solution of IVb in an excess of benzylamine was then heated under reflux until the ethanol formed by aminolysis could no longer be distilled from the solution. Benzylamine was removed by slow distillation. Distillation of the residue under reduced pressure yielded the imide V. Reduction of V to VI with lithium aluminum hydride was followed by catalytic debenzoylation, and 3-methyl-3,9-diazaspiro[5.5]undecane (VII) was obtained. To insure that both synthetic pathways had indeed produced the same spirane system, VII was treated with ethyl chloroformate. The product, 3-ethoxycarbonyl-9-methyl-3,9-diazaspiro[5.5]undecane (VIII), was reduced (LiAlH₄) to 3,9-dimethyl-3,9-diazaspiro[5.5]undecane (Ib). The dihydrochloric acid salt from samples of Ib prepared by routes A and B were identical, and a mixed melting point

gave no depression. The dimethiodides obtained from samples of Ib prepared by each route had a melting point of over 360° and gave identical infrared spectra. Treatment of VII with dimethylaminopropyl chloride in refluxing toluene afforded 3-(3-[dimethylamino]propyl)-9-methyl-3,9-diazaspiro[5.5]undecane (IX) in 74% yield. Repeating route A using dimethylaminopropylamine resulted in the analogous 3,9-bis(3-dimethylaminopropyl)derivative (Ic) of 3,9-diazaspiro[5.5]undecane.

EXPERIMENTAL (5)

3,9-Dimethyl-3,9-diazaspiro[5.5]undecane-2,4,8,10-tetrone (IIIa).

Methanetetraacetic acid dianhydride (15.0 g., 0.07 mole) was placed in a 100 ml. round bottom flask and 25% aqueous methylamine (50 ml.) was added. After a short period a clear solution was obtained, which was concentrated by heating in an oil bath and permitting the excess of methylamine and water to distill. The material solidified, then remelted on further heating. The melt was maintained at 260° for 30 min. and then poured into a mortar. After cooling, the material was ground to a powder. The powder was dissolved in 250 ml. of hot acetonitrile, treated with Norit, and filtered hot. After cooling, there was obtained 10 g. (67.5%) of a product, m.p. 244-245°. Recrystallization from acetonitrile raised the m.p. to 245-246°.

Anal. Calcd. for C₁₁H₁₄N₂O₄: C, 55.45; H, 5.92; N, 11.76. Found: C, 55.68; H, 6.09; N, 11.76.

3,9-Dimethyl-3,9-diazaspiro[5.5]undecane (Ib).

A 2 l. 3-necked flask fitted with a stirrer, a dropping funnel, and a condenser to which a drying tube was attached was charged with lithium aluminum hydride (15 g.) and 1 l. of anhydrous ether. A slurry of finely ground IIIa (9 g., 0.038 mole) in 200 ml. of ether was added, and the mixture was heated under reflux for 24 hr. Water (40 ml.) was added slowly, and after stirring for 1 hr., the mixture was filtered. The filtrate was dried over sodium sulfate, filtered and the solvent was removed by distillation. The residue was distilled under reduced pressure, yielding 2.5 g. (37.9%) of Ib, b.p. 130-134° (28 mm.). The dimethiodide, prepared from Ib with excess methyl iodide in refluxing ethanol and crystallized from aqueous methanol, had a m.p. higher than 360°.

Anal. Calcd. for C₁₃H₂₀I₂N₂: C, 33.49; H, 6.05; N, 6.01; I, 54.45. Found: C, 33.73; H, 6.08; N, 6.31; I, 54.33.

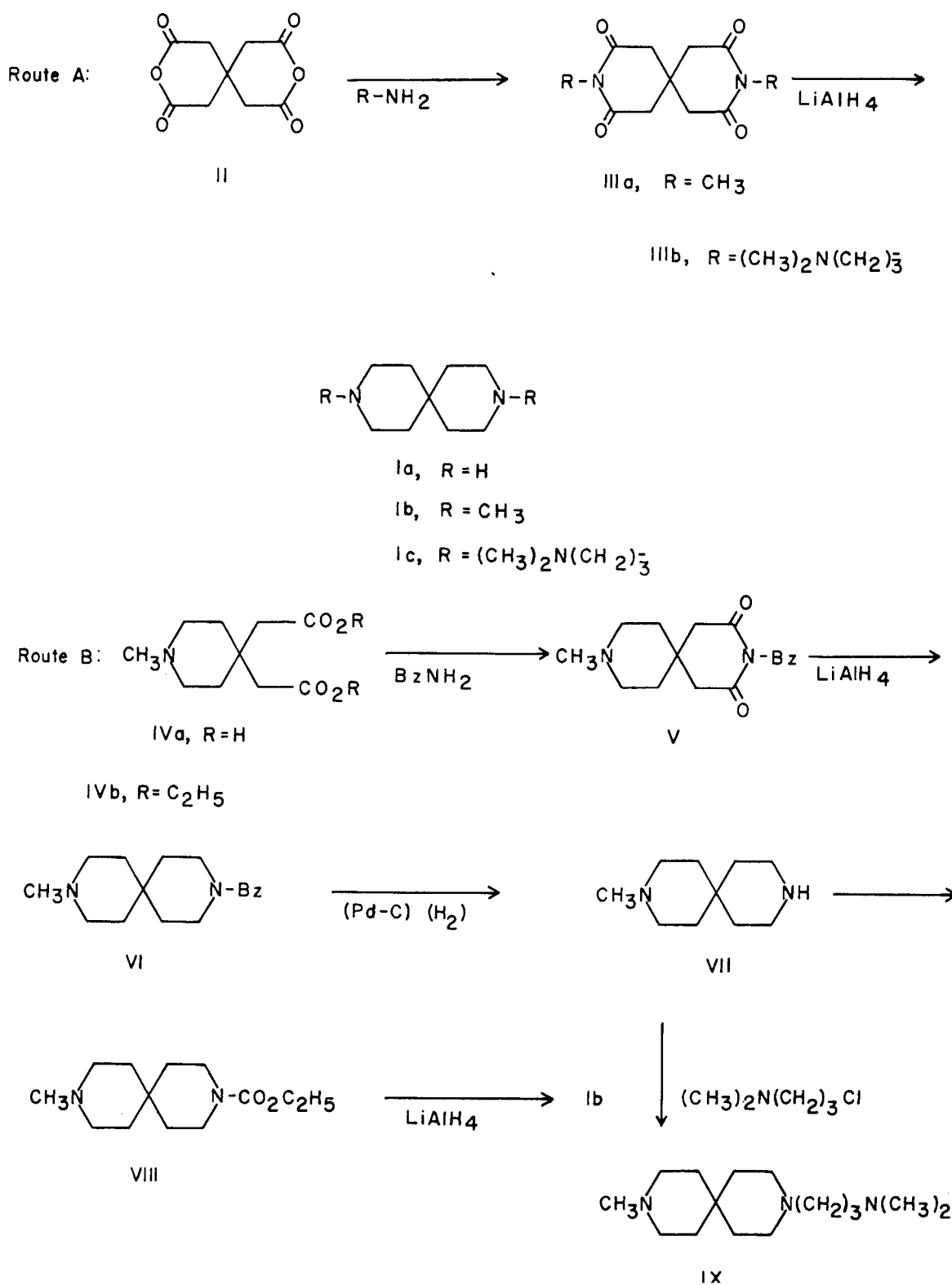
The dihydrochloride of Ib was obtained by treating a solution of the base in ethyl acetate with excess of alcoholic hydrogen chloride. The salt, recrystallized from propanol-ether and dried at 120°, had m.p. 333-334°.

Anal. Calcd. for C₁₁H₂₄Cl₂N₂: C, 51.76; H, 9.48; N, 10.98; Cl, 27.78. Found: C, 51.82; H, 9.30; N, 11.14; Cl, 27.63.

3,9-Di-(3-dimethylaminopropyl)-3,9-diazaspiro[5.5]undecane-2,4,8,10-tetrone (IIIb).

A mixture of dianhydride (II) (10 g., 0.047 mole) and 3-dimethylaminopropylamine (11 g., 0.1 mole) was heated at 250° for 30 min. Distil-

CHART I



lation through a short-path column at 0.01 mm. yielded the product (12.5 g., 70%), which solidified in the receiver.

Anal. Calcd. for $C_{13}H_{22}N_2O_4$: C, 59.97; H, 8.49; N, 14.73. Found: C, 59.78; H, 8.52; N, 14.55.

The dimethiodide had m.p. 272-274° (methanol). The dihydrochloride had m.p. 239-240° (acetonitrile-methanol).

3, 9-Di-(3-dimethylaminopropyl)-3, 9-diazaspiro[5.5]undecane (Ic).

A solution of the diimide IIb (9 g., 0.028 mole) in dry benzene was added slowly to a stirred suspension of lithium aluminum hydride (15 g.) in ether (500 ml.). The reaction mixture was stirred overnight, then decomposed with water and filtered. After drying, the filtrate was concentrated and the residue was distilled under reduced pressure, yielding 5 g. (67%) of Ic, b.p. 136-140° (0.025 mm.).

Anal. Calcd. for $C_{15}H_{40}N_4$: C, 70.31; H, 12.42; N, 17.27. Found: C, 70.30; H, 12.29; N, 17.36.

The tetrahydrochloride had m.p. 339-340° (methanol-water).

Anal. Calcd. for $C_{15}H_{44}Cl_4N_4$: Cl, 30.15. Found: Cl, 29.92.

1-Methylpiperidine-4, 4-diacetic acid (IVa).

The ammonium salt of 1, 5-dicyano-9-methyl-3, 9-diazaspiro[5.5]undecane-2, 4-dione (3) (230 g.) was suspended in 2 l. of 18% hydrochloric acid and refluxed for 24 hr. The solution was concentrated by distillation (atmospheric) to 750 ml. and then to dryness under vacuum. The dried residue was extracted repeatedly with boiling ethanol. The hot extracts were filtered and evaporated to dryness. The crude 1-methylpiperidine-4, 4-diacetic acid hydrochloride (178 g.) was recrystallized from 95% ethanol, yielding 154 g. (79%), m.p. 248-249°.

Anal. Calcd. for $C_{10}H_{18}ClNO_4$: Cl, 14.12; N, 5.57. Found: Cl, 14.04; N, 5.51.

Diethyl-1-methylpiperidine-4, 4-diacetate (IVb).

A well stirred suspension of IVa hydrochloride (125 g., 0.58 mole) in 1 l. absolute ethanol was saturated with dry hydrogen chloride. The solids dissolved and the solution was refluxed for 8 hr. Ethanol (600 ml.) was distilled from the solution and replaced by an equal volume of fresh ethanol. The solution was again saturated with hydrogen chloride, refluxed 4 hr., and concentrated to a small volume, a moderate vacuum (100 mm.) being applied near the end to avoid overheating. After cooling, the residue was taken up in ice water (250 ml.) and saturated with potassium carbonate. The oil layer was extracted into ether and the aqueous phase was extracted three times with ether. The combined extracts were dried over sodium sulfate, the ether was removed, and the residue was distilled under reduced pressure to give 76 g. (55%) of IVb, b.p. 122-125° (0.3 mm.).

Anal. Calcd. for $C_{14}H_{25}NO_4$: C, 61.96; H, 9.28; N, 5.16. Found: C, 62.28; H, 9.59; N, 5.11.

3-Benzyl-9-methyl-3, 9-diazaspiro[5.5]undecane-2, 4-dione (V).

A solution of IVb (140 g., 0.5 mole) in benzylamine (214 g., 2 mole) was placed in a 500 ml. flask fitted with a short (10 cm.) Vigreux column and distillation head. The solution was refluxed 24 hr. Ethanol was then removed by distillation followed by benzylamine, 100 ml. being collected. The remainder was distilled under reduced pressure yielding the product (85 g., 59%) as a viscous oil, b.p. 180-190° (0.1 mm.), which solidified on standing. The hydrochloride, prepared in acetone and recrystallized from acetone-methanol, had a m.p. 271-272°.

Anal. Calcd. for $C_{17}H_{23}ClN_2O_2$: C, 63.30; H, 7.18; Cl, 10.97; N, 8.68. Found: C, 63.08; H, 7.13; Cl, 10.88; N, 8.50.

3-Benzyl-9-methyl-3, 9-diazaspiro[5.5]undecane (VI).

A solution of V (245 g., 0.86 mole) in 750 ml. of dry ether was added slowly to a well stirred suspension of lithium aluminum hydride (68 g., 1.8 mole) in 2 l. of ether. The mixture was stirred and refluxed 16 hr. After decomposition with water (250 ml.), the mixture was filtered and the filter cake washed well with ether. The filtrate was dried, the solvent removed, and the residue distilled, yielding 185 g. (83.4%) of product, b.p. 137-143° (0.1 mm.).

Anal. Calcd. for $C_{17}H_{23}N_2$: C, 79.02; H, 10.14; N, 10.84. Found: C, 78.93; H, 10.06; N, 10.73.

The dihydrochloride of VI was prepared by passing dry hydrogen chloride into an ethereal solution of the base. After being twice recrystallized from ethanol-ether, the salt melted at 326-327°.

Anal. Calcd. for $C_{17}H_{23}Cl_2N_2$: Cl, 21.40. Found: Cl, 21.28.

Treatment of VI with excess methyl iodide in refluxing 2-propanol-ethyl acetate (1:1) produced, on cooling, a precipitate of the 3, 9-dimethiodide, m.p. 332-333° (dec., methanol).

Anal. Calcd. for $C_{15}H_{32}I_2N_2$: I, 46.81. Found: I, 46.62.

3-Methyl-3, 9-diazaspiro[5.5]undecane (VII).

A solution of VI (46 g., 0.17 mole) in methanol (200 ml.) was cooled, and concentrated hydrochloric acid (50 ml.) was added. The solution was placed in a hydrogenation apparatus with 10 g. of 10% palladium on carbon and was hydrogenated at 50 psi and 60°. When the hydrogenation was completed, the solution was cooled and filtered. The solvent was removed and the residue taken up in water, made strongly basic with sodium hydroxide, and extracted into ether. Distillation yielded 24.2 g. (84.6%) of VII, b.p. 128-130° (12 mm.). The product was a strong base which rapidly formed a carbonate on exposure to air.

Anal. Calcd. for $C_{10}H_{20}N_2$: C, 71.37; H, 11.98; N, 16.65. Found: C, 71.22; H, 11.87; N, 16.42.

The dihydrochloride, after recrystallization from ethanol-ether, melted at 319-320°.

Anal. Calcd. for $C_{10}H_{22}Cl_2N_2$: C, 49.80; H, 9.19; Cl, 29.39; N, 11.66. Found: C, 49.51; H, 9.03; Cl, 28.93; N, 11.73.

(3-Ethoxycarbonyl-9-methyl)-3, 9-diazaspiro[5.5]undecane (VIII).

To a cold, well stirred solution of VII (16.8 g., 0.1 mole) in 35 ml. of water was slowly added ethyl chloroformate (5.4 g., 0.05 mole), keeping the temperature between 10-15°. After 15 min., 4 ml. of 50% aqueous sodium hydroxide was added in portions, followed by the simultaneous dropwise addition of a second portion of ethyl chloroformate (5.4 g.) and 4 ml. of 50% sodium hydroxide. The mixture was stirred in the cold 30 min., then 5 ml. of 50% sodium hydroxide was added and the product was extracted into ether. The ethereal extract was washed with saline (5 ml.) and dried over sodium sulfate. The solvent was removed and the residue was distilled under pressure, yielding 14 g. (58%) of VIII, b.p. 126-130° (0.2 mm.), n_D^{20} 1.4940.

Anal. Calcd. for $C_{13}H_{24}N_2O_2$: C, 65.00; H, 10.07; N, 11.67. Found: C, 64.80; H, 10.15; N, 11.57.

3, 9-Dimethyl-3, 9-diazaspiro[5.5]undecane (Ib).

A solution of VIII (12 g., 0.05 mole) in 25 ml. of ether was added to a stirred suspension of lithium aluminum hydride (1.9 g.) in 150 ml. of ether. A vigorous reaction ensued. After 1 hr., the reaction mixture was quenched by the addition of 6 ml. of water and filtered. The filtrate was dried and concentrated, and the product was distilled, yielding 5.7 g. (62.7%) of Ib, b.p. 137-139° (28 mm.), n_D^{25} 1.4865.

Anal. Calcd. for $C_{11}H_{22}N_2$: C, 72.50; H, 12.17; N, 15.38. Found: C, 72.13; H, 12.27; N, 15.22.

The dihydrochloride had a m.p. of 333-334° (ethanol). A dimethiodide was obtained by refluxing 2 g. of Ib in 50 ml. of ethanol with 5 ml. of methyl iodide. The precipitate, after being filtered from the solution, washed with ethanol, and dried, had a m.p. higher than 360°.

Anal. Calcd. for $C_{13}H_{26}I_2N_2$: C, 33.49; H, 6.05; I, 54.45; N, 6.01. Found: C 33.65; H, 5.98; I, 54.20; N, 5.91.

3-(3-Dimethylamino)propyl-9-methyl-3, 9-diazaspiro[5.5]undecane (IX).

A solution of 3-methyl-3, 9-diazaspiro[5.5]undecane (4.2 g., 0.025 mole), 3-dimethylaminopropyl chloride (3 g., 0.025 mole), and potassium iodide (0.2 g.) in 30 ml. of toluene was heated under reflux for 8 hr. Dry hydrogen chloride was passed into the cooled solution, which was then diluted with 3 volumes of dry ether. The precipitate was filtered, yielding 7 g. (74%) of IX as the trihydrochloride. Recrystallization from ethanol gave a product melting at 318-319°.

Anal. Calcd. for $C_{15}H_{34}Cl_3N_3$: Cl, 29.31; N, 11.58. Found: Cl, 29.11; N, 11.39.

REFERENCES

- (1) Presented before the Division of Organic Chemistry at the 147th National Meeting of the American Chemical Society, Philadelphia, Pennsylvania, April, 1964.
- (2) J. B. Clements and L. M. Rice, *J. Org. Chem.*, **24**, 1958 (1959); L. M. Rice and C. H. Grogan, *ibid.*, **26**, 54 (1961); L. M. Rice, C. G. Geschickter, and C. H. Grogan, *J. Med. Chem.*, **6**, 388 (1963).
- (3) C. K. Ingold and L. C. Nickolls, *J. Chem. Soc.*, 1638 (1922).
- (4) S. M. McElvain and R. E. Lyle, Jr., *J. Am. Chem. Soc.*, **72**, 384 (1950).
- (5) Melting points were taken on a Hoover-Thomas melting point apparatus and are corrected.

Received April 27, 1964

Washington, D.C., and Radno, Pa.