determined, but it was obvious that the desired lactone was not obtained.

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 71.99, 72.16; H, 9.07, 9.16.

The infrared spectrum of a Nujol mull indicated a hydroxyl group as well as a γ-lactone.

Preparation of the Lactone of 2-(1-Hydroxycyclohexyl)-6-cyclohexene-1-carboxylic Acid (IXb) from the Dehydration of the *cis*-Lactone of 2-(1-Hydroxycyclohexyl)-1-hydroxycyclohexanecarboxylic Acid (VIIIb).—To a solution of 50 g. (0.223 mole) of VIIIb in 150 ml. of dry pyridine was added, cautiously, 50 ml. of thionyl chloride according to the general procedure of Boekelheide and Schilling.[2a] The mixture was heated overnight on a steam-bath, cooled and poured into ice-water. Ether extraction gave 33 g. (72%) of product, m.p. 67–69°. An analytical sample obtained by several recrystallizations from petroleum ether (b.p. 30–60°) melted at 71–72°, λ_{max}^{MeOH} 220 mμ, ϵ_{max} 11,100. The melting point was depressed, m.p. 63–64°, on admixture with IXa. The infrared spectrum in Nujol mull indicated an unsaturated γ-lactone. The spectrum was distinctly different from IXa.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.90; H, 8.54.

Preparation of the Lactone of 2-(1-Hydroxycyclohexyl)-1-cyclohexene-1-carboxylic Acid (IXa) from the Dehydration of the *trans*-Lactone of 2-(1-Hydroxycyclohexyl)-1-hydroxycyclohexanecarboxylic Acid (VIIIA).—To a solution of 2.0 g. (0.0089 mole) of VIIIa in 10 ml. of dry pyridine was added 4 ml. of thionyl chloride. The reaction was carried out as described above to give 1.65 g. (90%) of product, m.p. 68–75°. An analytical sample obtained by several recrystallizations from petroleum ether (b.p. 30–60°) melted at 79–80°. It was found to be identical (mixed melting point 79–80°, ultraviolet and infrared spectra) with IXa obtained from the reduction of the lactone of 2-(1-hydroxycyclohexyl)-1,4-cyclohexadiene-1-carboxylic acid (VI).

Preparation of the *cis*-Lactone of 2-(1-Hydroxycyclohexyl)-cyclohexanecarboxylic Acid (IIIb) from the Reduction of the Lactone of 2-(1-Hydroxycyclohexyl)-6-cyclohexene-1-carboxylic Acid (IXB).—A solution of 33 g. (0.160 mole) of IXb in 500 ml. of ethanol was reduced, using 10 g. of Raney nickel catalyst at 150° and 100 atmospheres of hydrogen. The totally reduced material was recovered to give 25 g. (75%) of an oil which solidified on standing, m.p. 50–52°. An analytical sample obtained by several recrystallizations from petroleum ether (b.p. 30–60°) melted at 55–56° with no appreciable ultraviolet absorption between 400 and 215 mμ. It was found to be identical (mixed melting point, 55–56° and infrared spectra) with IIIb obtained from the reduction of IXa.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68; mol. wt., 208. Found: C, 74.76; H, 9.52; mol. wt., 213 (cryoscopic).

Preparation of *cis*-2-(1-Hydroxycyclohexyl)-cyclohexanemethanol (Vb).—A solution of 1.00 g. (0.0048 mole) of IIIb was reduced with lithium aluminum hydride as described above to give 1.00 g. (98%) of glycol. Recrystallization from hexane gave a solid, m.p. 117–118°.

Anal. Calcd. for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.42; H, 11.12.

The infrared spectrum in a Nujol mull indicated a hydroxyl group and was distinctly different from the spectrum of the *trans* isomer Va.

Isomerization of the *cis*-Lactone of 2-(1-Hydroxycyclohexyl)-cyclohexanecarboxylic Acid (IIIb).—A solution containing 0.104 g. (0.0005 mole) of the *cis*-lactone of 2-(1-hydroxycyclohexyl)-cyclohexanecarboxylic acid was isomerized as described for the *trans* isomer to give 0.047 g. (45%) of liquid. The infrared spectrum in carbon disulfide indicated it to be a mixture consisting of 10% of the *trans*- and 90% of the *cis*-lactones of 2-(1-hydroxycyclohexyl)-cyclohexanecarboxylic acid, identical to that obtained from the isomerization of the *trans*-lactone IIIa.

BROOKLYN 1, NEW YORK

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Antispasmodics. IX. 1-Azaspiro[4.5]decane and Derivatives[1]

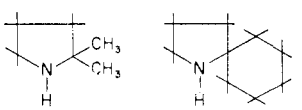
BY ROBERT BRUCE MOFFETT

RECEIVED FEBRUARY 13, 1957

Previous studies in these laboratories have demonstrated that certain compounds containing 2,2-dimethylpyrrolidine (I) are particularly potent anticholinergics. The structurally similar compound, 1-azaspiro[4.5]decane (II), has now been prepared, in which the two methyl groups are joined in a ring. This was incorporated into a variety of compounds of types known to be in general powerful anticholinergics (VIII, IX and XII); however, they had surprisingly little of this type of activity.

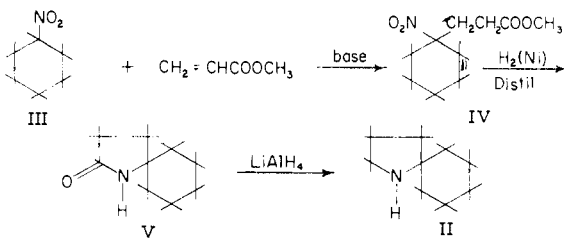
A considerable number of compounds containing the pyrrolidine group have been studied in these laboratories.[2] Of these the 2,2-dimethylpyrrolidine group (I) has been found to be particularly potent when combined, for example, in esters of the type generally used in antispasmodics.[2c]

In extending this work we have investigated the effect of joining the two methyl groups in a ring thus creating the spiro structure, 1-azaspiro[4.5]-decane (II).

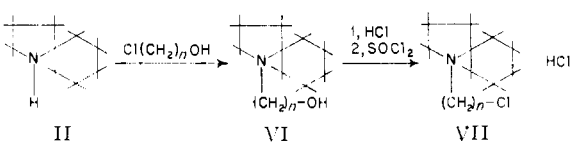


I II

This was accomplished by a modification of the synthesis used for 2,2-dimethylpyrrolidine.[2b]



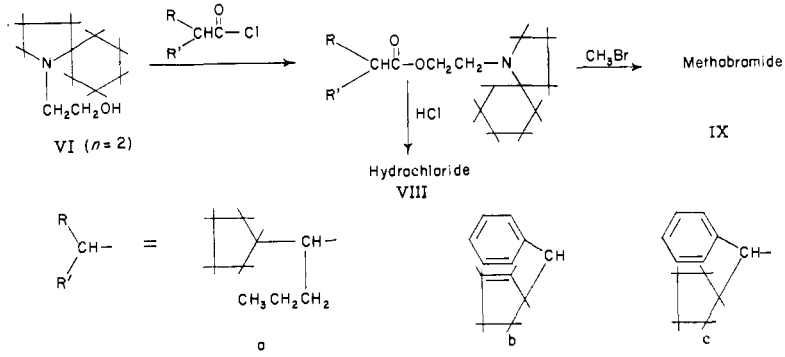
This spiropyrrolidine was allowed to react with ethylene chlorohydrin and with trimethylene chlorohydrin to give the corresponding 1-(hydroxy-



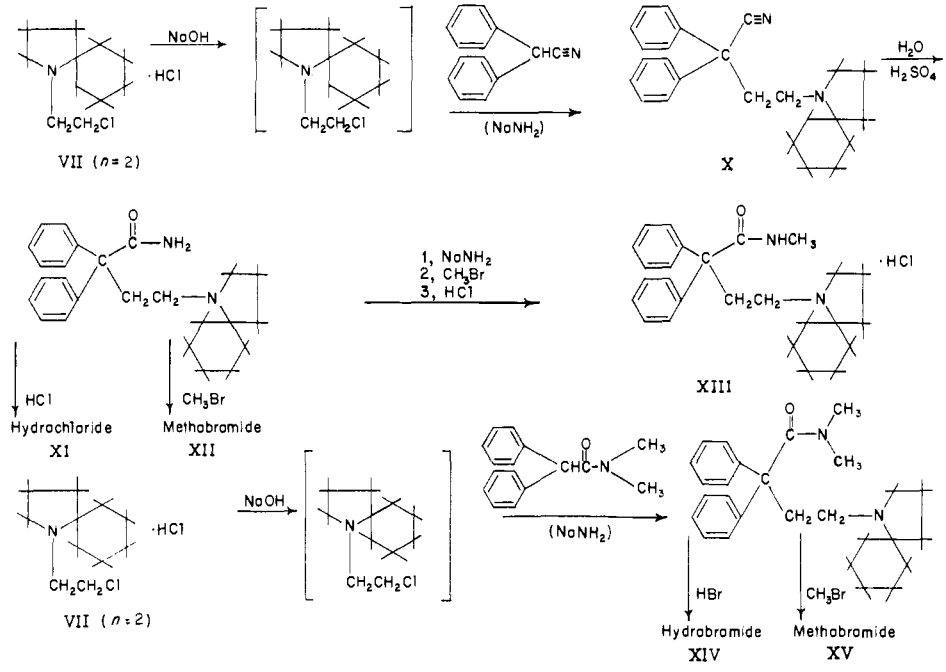
(1) Presented before the Division of Medicinal Chemistry, A.C.S., at Atlantic City, New Jersey, September, 1956, Abstracts, page 4-N.

(2) (a) R. B. Moffett, *et al.*, *J. Org. Chem.*, **14**, 862 (1949); (b) **17**, 407 (1952); (c) THIS JOURNAL, **77**, 1565 (1955), and preceding papers in this series.

alkyl)-azaspiro[4.5]decane (VI). These in turn were converted to the corresponding chloride hydrochlorides VII with thionyl chloride. The ethanol derivative (VI, $n=2$) was allowed to react with the acid chlorides of several acids which had previously given good anticholinergics.[2c]



The chlorethyl intermediate was used to alkylate diphenylacetonitrile and the product hydrolyzed to give amides of the type known to include powerful anticholinergics.[3] The mono- and dimethylamides also were prepared.



A few analogs of the phenothiazine antihistamines,[4] antispasmodics[5] and tranquilizing drugs[6] were also prepared.

Pharmacology.—These spiro compounds were tested as anticholinergics both in Thiry-Vella dogs and for their ability to block the depressor response of methacholine in anesthetized dogs. In comparison with structurally related potent anticholinergics such as 2-(2,2-dimethyl-1-pyrrolidyl)-ethyl cyclopentylvalerate hydrochloride (atropine index 1.2)[2c] and α,α-diphenyl-γ-(2,2-dimethyl-1-pyrrolidyl)-butyramide methobromide[7] (atropine index 4), their activities proved to be somewhat lower than anticipated. Compound XII had an atropine index of about 0.5 in Thiry-Vella dogs while the rest had indexes of less than 0.15.

These compounds have been screened in a variety of other pharmacological tests. Preliminary data appear interesting and detailed results will be published elsewhere.

Acknowledgments.—The author is indebted to Dr. Patrick H. Seay, Dr. Walter A. Freyburger and associates of the Department of Pharmacology for the pharmacological results, and to Dr. Richard V. Heinzelman of the Department of Chemistry for guidance.

Experimental[8]

Methyl β-(1-Nitrocyclohexane)-propionate (IV).—To a mixture of 333 g. (2.55 moles) of nitrocyclohexane (du Pont technical grade redistilled), 300 ml. of dioxane (treated with lithium aluminum hydride and redistilled) and 30 ml. of a 35% methanolic solution of benzyltrimethylammonium

(3) M. Bockemühl and G. Ehrhart, *Ann.*, **561**, 52 (1948).

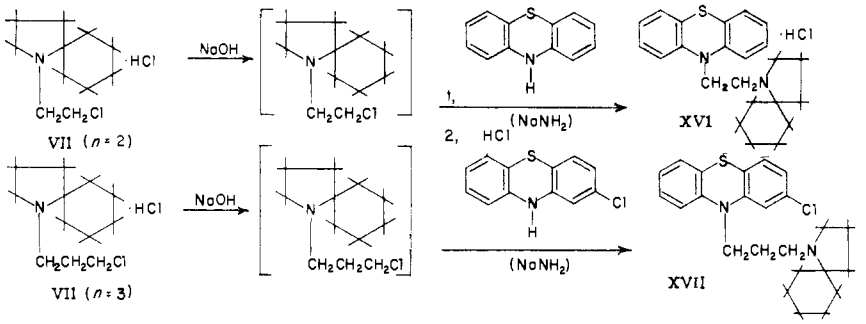
(4) W. B. Reid, J. B. Wright, H. G. Kolloff and J. H. Hunter, THIS JOURNAL, **70**, 3, 100 (1948).

(5) R. A. Robinson and J. W. Cusic, U. S. Patent 2,590,125 (1952).

(6) P. Viaud, *J. Pharm. Pharmacol.*, **6**, 361 (1954).

(7) R. B. Moffett and B. D. Aspergren, U. S. Patent 2,782,206 (1957).

(8) Elemental analyses are by Mr. William A. Struck and staff of our Analytical Chemistry Laboratory.



hydroxide was added with stirring during about 15 minutes 227.5 g. (2.55 moles) of methyl acrylate (redistilled). The temperature rose to about 100° and then dropped to about 55°. The mixture was then heated on a steam-bath with stirring for 3 hours, diluted to about 1 l. with ether, acidified with dilute hydrochloric acid and washed well with saturated sodium chloride solution. After drying over sodium sulfate the solution was distilled through a Vigreux column. The product distilled at 96.5° (0.05 mm.) to 124.5° (0.35 mm.); yield 532 g. (96.8%); $n^{25}D$ 1.4710.

A sample redistilled through a short packed column gave a middle fraction of colorless liquid; b.p. 96° (0.025 mm.) $n^{25}D$ 1.4711.

Anal. Calcd. for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 56.05; H, 8.02; N, 6.48.

1-Azaspiro[4.5]decan-2-one (V).[9]—A solution of 453.3 g. (2.11 moles) of methyl β-(1-nitrocyclohexane)-propionate in 1.26 l. of ethanol was hydrogenated in three runs with 11 tsp. of Raney nickel catalyst overnight at 50°. After filtration and distillation of the solvent the white crystalline residue was dissolved by boiling with 2 l. of methylcyclohexane and about 100 ml. of this solvent was distilled to remove alcohol or water. The hot solution was filtered and on cooling it gave 253 g. of white crystals, m.p. 131–133°. By concentrating the filtrate an additional 31.4 g. of crystals, m.p. 129–132°, were obtained. The total yield was 88.2%. A sample recrystallized from petroleum hexane had m.p. 132–133°. It can be readily sublimed at 100–135° (0.012 mm.). It is a very weak base, moderately soluble in water and very soluble in dilute mineral acids.

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.45; H, 9.85; N, 9.03.

1-Azaspiro[4.5]decane (II).—A mixture of 95 g. (2.5 moles) of lithium aluminum hydride and 1.5 l. of tetrahydrofuran (distilled from lithium aluminum hydride) in a 12-l. flask was refluxed with stirring for a few minutes and then a solution of 206 g. (1.343 moles) of the above spiropyrrolidone in 1.1 l. of tetrahydrofuran was added slowly, and the mixture was heated under reflux on a steam-bath with stirring for 18 hours. About 2 l. of solvent was distilled at atmospheric pressure. Then were added slowly in succession: 1 l. of ether, 200 ml. of ethyl acetate and 1 l. of concentrated hydrochloric acid in 1.5 l. of water. The strongly acidic solution was steam distilled until the boiling point reached 100°. A 50% aqueous solution containing 680 g. of sodium hydroxide was added and the mixture was again steam distilled until practically no more basic material was coming over. About 4 l. of distillate was collected which separated into two layers. This was extracted twice with ether and then continuously extracted with ether for 6 hours. The ether solutions were well dried by shaking with potassium carbonate. After filtration the solution was distilled through an efficient column. After removing the solvent the fraction boiling at 99–104° (42 mm.) was collected; yield, 84%; $n^{25}D$ 1.4817. A sample was redistilled giving a middle fraction of colorless liquid, b.p. 96° (33 mm.), $n^{25}D$ 1.4814.

Anal. Calcd. for $C_9H_{17}N$: C, 77.63; H, 12.31; N, 10.06; equiv. wt., 139.24. Found: C, 77.95; H, 11.88; N, 9.24; equiv. wt., 140.16.

1-(β-Hydroxyethyl)-1-azaspiro[4.5]decane (VI, $n = 2$).—A mixture of 146.6 g. (1.05 moles) of 1-azaspiro[4.5]decane and 64.6 g. (0.8 mole) of ethylene chlorohydrin was stirred and heated under reflux to 120°. The heating was stopped but the temperature spontaneously rose to about 167°. When the temperature had dropped to 120° the flask was again heated at 130–150° for 15 minutes. After cooling an excess of 50% aqueous sodium hydroxide was added and the product was thoroughly extracted with ether. The ether solution was well dried over potassium carbonate, filtered, and the ether was removed by distillation. The product was distilled through a short column. After removing a forerun consisting mostly of unreacted 1-azaspiro[4.5]decane, the main fraction distilled, b.p. 138° (12 mm.). The yield was 126.2 g. (86.2%) of colorless liquid; $n^{25}D$ 1.5010.

Anal. Calcd. for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 72.41; H, 11.87; N, 7.66.

Hydrochloride.—Hydrogen chloride gas was passed into a cooled benzene solution of the above free base. The hydrochloride separated in crystalline form but tended to redissolve if a large excess of hydrogen chloride was used. A sample was recrystallized from isopropyl alcohol giving white crystals, m.p. 177.5–179°.

Anal. Calcd. for $C_{11}H_{22}ClNO$: Cl, 16.13. Found: Cl, 16.30.

1-(β-Chloroethyl)-1-azaspiro[4.5]decane Hydrochloride (VII, $n = 2$).—A slight excess of hydrogen chloride gas was passed into a cooled, stirred solution of 121 g. (0.676 mole) of 1-(β-hydroxyethyl)-1-azaspiro[4.5]decane in 250 ml. of benzene. The flask was surrounded by an ice-bath, and 60 ml. (0.88 mole) of thionyl chloride was added slowly with stirring. The solid completely dissolved. The solution was then heated on a steam-bath with stirring for 2 hours during which the product separated in crystalline form. After cooling, it was collected, washed with benzene and absolute ether and dried giving 158.0 g. (98.0%) of nearly white crystals, m.p. 239–240°.

A sample was recrystallized from isopropyl alcohol, m.p. 239–240°.

Anal. Calcd. for $C_{11}H_{21}Cl_2N$: Cl, 29.77. Found: Cl, 29.50.

1-(γ-Hydroxypropyl)-1-azaspiro[4.5]decane (VI, $n = 3$).—This was prepared by a procedure similar to that used for 1-(β-hydroxyethyl)-azaspiro[4.5]decane above using 27.84 g. (0.2 mole) of 1-azaspiro[4.5]decane and 18.9 g. (0.2 mole) of trimethylene chlorohydrin. A yield of 23.43 g. (59.5%) of colorless liquid, b.p. 155° (11.5 mm.), $n^{25}D$ 1.4979, was obtained.

Anal. Calcd. for $C_{12}H_{23}NO$: C, 73.21; H, 11.75; N, 7.10. Found: C, 74.13, 74.35; H, 11.98, 12.13; N, 7.12.

1-(γ-Chloropropyl)-1-azaspiro[4.5]decane Hydrochloride (VII, $n = 3$).—This was prepared by a procedure similar to that used for 1-(β-chloroethyl)-1-azaspiro[4.5]decane hydrochloride above using 22.4 g. (0.1135 mole) of 1-(γ-hydroxypropyl)-1-azaspiro[4.5]decane, 50 ml. of benzene and 15 ml. (0.2 mole) of thionyl chloride. The product consisted of 26.8 g. (93.6%) of white crystals, m.p. 224–226.5°.

A sample was recrystallized from isopropyl alcohol, m.p. 225–227°.

Anal. Calcd. for $C_{12}H_{23}Cl_2N$: Cl, 28.11. Found: Cl, 28.07

Cyclopentyl-*n*-propylacetate Ester of 1-(β-Hydroxyethyl)-1-azaspiro[4.5]decane Hydrochloride (VIIIa).—To a solution of 9.33 g. (0.05 mole) of 1-(β-hydroxyethyl)-1-azaspiro-[4.5]decane in 50 ml. of dry benzene was added 11.3 g. (0.06 mole) of cyclopentyl-*n*-propylacetyl chloride.[10] A white

(9) Swiss Patent 227,125 (1943).

(10) R. B. Moffett, C. A. Hart and J. Neil, *J. Org. Chem.*, **15**, 343 (1950).

precipitate separated almost immediately but redissolved on heating under reflux for 3 hours. The red solution was treated with 30 ml. of 10% aqueous sodium hydroxide and extracted well with ether. After washing with water the ether was removed and the product was distilled. A middle fraction of 8.34 g., b.p. 146–147° (0.04 mm.), was dissolved in absolute ether, made acidic with ethanolic hydrogen chloride and further diluted with absolute ether. The hydrochloride was obtained as a white crystalline material, m.p. 151–152°; weight 8.2 g.

Anal. Calcd. for $C_{21}H_{38}ClNO_2$: C, 67.80; H, 10.30; Cl, 9.53. Found: C, 68.21; H, 10.16; Cl, 9.53.

Free Base.—The filtrate from the above hydrochloride was reconverted to the free base, combined with the lower and higher boiling fractions from the distillation and redistilled. A yield of 7.0 g. of nearly colorless oil was obtained, b.p. 146° (0.05 mm.); $n^{25}D$ 1.4879. The total yield of hydrochloride and free base amounted to 85.8%.

Anal. Calcd. for $C_{21}H_{37}NO_2$: C, 75.17; H, 11.12; N, 4.17. Found: C, 76.15, 76.53; H, 10.93, 11.16; N, 4.00.

Methobromide (IXa).—To a cold solution of 6.5 g. (0.0194 mole) of the above free base in 25 ml. of methyl ethyl ketone was added 6.2 g. of cold methyl bromide. The flask was stoppered, clamped and allowed to stand at room temperature for 2 days. Crystals separated and were collected, washed with methyl ethyl ketone and dried giving 5.06 g. (60.6%) of product, m.p. 152–153°. A small additional yield was obtained from the filtrate.

Anal. Calcd. for $C_{22}H_{40}BrNO_2$: C, 61.38; H, 9.37; Br, 18.57. Found: C, 61.64; H, 9.34; Br, 18.58.

Phenyl-Δ^2-cyclopentenylacetate Ester of 1-(β-Hydroxyethyl)-1-azaspiro[4.5]decane.—This was prepared by a procedure similar to that used for the above ester using 11.6 g. (0.0634 mole) of 1-(β-hydroxyethyl)-azaspiro[4.5]decane, 50 ml. of dry benzene and 15.5 g. (0.07 mole) of phenyl-Δ^2-cyclopentenylacetyl chloride.[11] The product was distilled giving 22.17 g. (95%) of viscous light yellow liquid, b.p. 163° (0.01 mm.).

Anal. Calcd. for $C_{24}H_{33}NO_2$: C, 78.43; H, 9.05; N, 3.81. Found: C, 78.80; H, 8.88; N, 3.84.

Hydrochloride (VIIb).—To a solution of 16.3 g. (0.0444 mole) of the above free base in absolute ether was added a slight excess of ethanolic hydrogen chloride. Dilution with more ether caused the hydrochloride to separate as an oil. The solvent was removed by distillation under reduced pressure below 90° and the glassy residue was crystallized from ethyl acetate giving 12.7 g. (71%) of white crystals, m.p. 140–142°.

Anal. Calcd. for $C_{24}H_{34}ClNO_2$: C, 71.33; H, 8.48; Cl, 8.78. Found: C, 71.31; H, 8.37; Cl, 8.96.

Methobromide (IXb).—To a cold solution of 4.55 g. (0.0124 mole) of the above free base in 25 ml. of methyl ethyl ketone was added 5 g. of cold methyl bromide. The flask was stoppered, clamped and allowed to stand at room temperature for 5 days. White crystals separated and were collected, washed with methyl ethyl ketone and then with absolute ether and dried; yield 5.0 g. (87.2%); m.p. 167.5–169°.

Anal. Calcd. for $C_{25}H_{36}BrNO_2$: C, 64.92; H, 7.85; Br, 17.28. Found: C, 65.01; H, 7.98; Br, 17.49.

Phenylcyclopentylacetate Ester of 1-(β-Hydroxyethyl)-1-azaspiro[4.5]decane Hydrochloride (VIIIc).—A solution of 9.47 g. (0.0234 mole) of the above hydrochloride in 150 ml. of 95% ethanol was hydrogenated at room temperature and 40 lb. pressure with 0.1 g. of platinum oxide catalyst. The theoretical amount of hydrogen was taken up in 10 minutes. The solution was filtered from the catalyst and distilled nearly to dryness below 40° under reduced pressure. The residue crystallized from ethyl acetate on the addition of ether, giving 7.88 g. (83%) of white crystals, m.p. 152–153.5°.

Anal. Calcd. for $C_{24}H_{36}ClNO_2$: C, 70.99; H, 8.94; Cl, 8.73. Found: C, 71.21; H, 8.99; Cl, 8.77.

α,α-Diphenyl-γ-[1-(1-azaspiro[4.5]decane)]-butyronitrile (X).—A mixture of 38.6 g. (0.2 mole) of diphenylacetonitrile, 300 ml. of dry toluene and 5.06 g. (0.22 mole) of lithium amide was heated under reflux under nitrogen with vigorous stirring for 4 hours.

A solution of 1-(β-chloroethyl)-1-azaspiro[4.5]decane was prepared by shaking 85.9 g. (0.36 mole) of the hydrochloride with ice and 35 ml. of 50% aqueous sodium hydroxide. The mixture was extracted five times with toluene, the toluene solution was well dried over potassium carbonate, and made up to 400 ml.

An aliquot of 244.5 ml. (equivalent to 0.22 mole) of the toluene solution of the chloride was added dropwise with stirring during 30 minutes to the above suspension of lithium salt of diphenylacetonitrile. The mixture was then heated under reflux with stirring for 19 hours. After cooling the mixture was washed with water and the aqueous washings were extracted with ether. The combined ether and toluene solutions were shaken with dilute hydrochloric acid which caused the separation of the hydrochloride as an oily layer insoluble in both the water and toluene. The hydrochloride and aqueous layers were separated, washed with ether and made basic with dilute sodium hydroxide. The free base was extracted with ether and benzene and after washing with water the solvent was removed. The product was distilled giving 46.3 g. of light brown viscous liquid, b.p. 160° (0.02 mm.). On standing, it crystallized and was recrystallized from isopropyl alcohol giving 33.85 g. (47.2%) of white crystals, m.p. 85–90°. A sample was recrystallized again, m.p. 90–92°.

Anal. Calcd. for $C_{25}H_{30}N_2$: C, 83.75; H, 8.44; N, 7.82. Found: C, 83.95; H, 8.45; N, 7.80.

Hydrochloride.—The above moist toluene and ether solutions, from which the oily hydrochloride had separated, on standing deposited white crystals; weight 5.56 g. (7%). This was recrystallized from isopropyl alcohol giving 5.35 g. of white crystals which on slow heating in m.p. tube melted at 123–128° with foaming, then crystallized and remelted at 195–197°. Infrared spectrum and analysis shows this to be a hydrate.

Anal. Calcd. for $C_{25}H_{31}ClN_2 \cdot 2H_2O$: C, 69.67; H, 8.19; Cl, 8.42; N, 6.50; H_2O, 8.36. Found: C, 71.19; H, 8.42; Cl, 8.22; N, 6.80; H_2O (loss of wt. on drying), 8.56.

Calcd. for $C_{25}H_{31}ClN_2$: C, 76.01; H, 7.91. Found (on dried sample): C, 75.74; H, 8.04.

α,α-Diphenyl-γ-[1-(1-azaspiro[4.5]decane)]-butyramide.—A solution of 32.8 g. (0.0915 mole) of the above nitrile free base in 5.5 ml. of concentrated sulfuric acid and 55 ml. of water was heated with stirring on a steam-bath for 4 hours. After standing overnight the solution was poured onto ice giving an oily sulfate salt which dissolved in the aqueous phase on the addition of ether. The aqueous layer was extracted again with ether and the ether solutions were washed with water. The combined aqueous fractions were made basic with ammonium hydroxide giving an oil which soon crystallized. The crude product was recrystallized from 500 ml. of 80% ethanol giving 22.95 g. (66.8%) of crystals, m.p. 169.5–172°.

Anal. Calcd. for $C_{25}H_{32}N_2O$. C, 79.74; H, 8.57; N, 7.44. Found. C, 79.84; H, 8.32; N, 7.40.

Hydrochloride (XI).—A solution of 6.5 g. (0.0173 mole) of the above free base in methanol and 1.6 ml. of concentrated aqueous hydrochloric acid was concentrated on a steam-bath by a stream of nitrogen. Benzene was added and the solution was further concentrated. On cooling it crystallized giving 7.3 g. of white crystalline powder, m.p. 212.5–214.5° (heated slowly in m.p. tube). A sample in a tube placed in the bath at 175° immediately melted, placed in the bath at 160° it partly melted, and placed in the bath at 155° it did not melt.

Anal. Calcd. for $C_{25}H_{33}ClN_2O$: C, 72.70; H, 8.05; Cl, 8.59. Found: C, 72.77; H, 8.12; Cl, 8.63.

Methobromide (XII).—To a cold suspension of 7.53 g. (0.02 mole) of the above free base in 50 ml. of methanol was added 16 g. of cold methyl bromide. The flask was stoppered, clamped and allowed to stand at room temperature for 4 days, during which the starting material completely dissolved. The solution was concentrated and diluted with ether giving a gum. This was dissolved in methanol, filtered, concentrated and diluted with methyl ethyl ketone. On boiling on a steam-bath it crystallized giving 8.84 g. (93.7%) of white crystals, m.p. 200–202°.

Anal. Calcd. for $C_{26}H_{35}BrN_2O$: C, 66.23; H, 7.48; Br, 16.95. Found: C, 66.14; H, 7.52; Br, 16.56.

(11) R. Horclois, *Chimie et Industrie*, Special No. p. 357 (April, 1954).

α,α-Diphenyl-γ-[1-(1-azaspiro[4.5]decane)]-N-methylbutyramide Hydrochloride (XIII).—A suspension of 8.28 g. (0.022 mole) of the above amide free base and 0.97 g. (0.025 mole) of sodium amide in 75 ml. of dry toluene was heated under reflux with stirring for 2 hours. After cooling in an ice-bath, a solution of 2.3 g. (0.024 mole) of methyl bromide in 35 ml. of cold toluene was added dropwise with stirring during 30 minutes. The mixture was stirred at room temperature for 3 hours, cooled and extracted with dilute hydrochloric acid. The solution was made basic with sodium hydroxide giving an oily free base which was extracted out with ether and washed with water, and dried. A slight excess of ethanolic hydrogen chloride was added giving a gummy hydrochloride which crystallized on standing. This was recrystallized from methyl ethyl ketone giving 5.95 g. (63.4%) of white crystals, m.p. 186–188°.

Anal. Calcd. for $C_{26}H_{35}ClN_2O$: C, 73.13; H, 8.26; Cl, 8.30. Found: C, 73.29; H, 7.96; Cl, 8.33.

α,α-Diphenyl-γ-[1-(azaspiro[4.5]decane)]-N,N-dimethylbutyramide.—A mixture of 14.4 g. (0.06 mole) of diphenyl-N,N-dimethylacetamide,[12] 100 ml. of dry toluene and 2.65 g. (0.068 mole) of sodium amide was heated for 2 hours under reflux, under nitrogen with vigorous stirring. After cooling, 72.2 ml. (equivalent to 0.065 mole) of a toluene solution of 1-(β-chloroethyl)-1-azaspiro[4.5]decane (see above under preparation of the nitrile) was added dropwise with stirring during 20 minutes. The mixture was then heated under reflux for 1 hour and allowed to stand overnight. It was washed with water, the washings were extracted with ether, and the ether and toluene solutions were extracted with dilute hydrochloric acid. The extracts were washed with ether and made basic with dilute sodium hydroxide giving a gummy free base which soon crystallized to 23.7 g. of light yellow solid, m.p. 133–145°. This was recrystallized from isopropyl alcohol giving 17.8 g. of nearly white crystals, m.p. 147–152°. Recrystallization from benzene gave 11.32 g. (46.6%) of white crystals, m.p. 149–152°.

Anal. Calcd. for $C_{27}H_{36}N_2O$: C, 80.15; H, 8.97; N, 6.93. Found: C, 80.44; H, 8.93; N, 6.87.

Hydrobromide (XIV).—The filtrates from the recrystallization of the free base were acidified with 48% hydrobromic acid and concentrated. Ether was added giving a gum which solidified on standing. This was dissolved in methyl ethyl ketone and concentrated. Acetone was added and crystals immediately separated. This was recrystallized from methyl ethyl ketone giving 5.7 g. (17.5%) of white crystals, m.p. about 103–110° dec. The total yield of free base and hydrobromide was 64.1%.

This appeared to be a solvate so a 0.1-g. sample in a little ethanol was treated with 2,4-dinitrophenylhydrazine solution giving a 2,4-dinitrophenylhydrazone. This was recrystallized from ethanol, m.p. 116–121°. A mixed melting point with authentic acetone 2,4-dinitrophenylhydrazone (m.p. 125–127°) gave no depression (mixed m.p. 118–124°). A mixed melting point with authentic methyl ethyl ketone 2,4-dinitrophenylhydrazone (m.p. 111–112°) gave a good depression (mixed m.p. 100–102°).

Anal. Calcd. for $C_{27}H_{37}BrN_2O \cdot CH_3COCH_3$: C, 66.28; H, 7.97; Br, 14.70. Found: C, 66.48; H, 7.77; Br, 14.59.

Methobromide (XV).—To a cold suspension of 8.09 g. (0.02 mole) of the free base in 25 ml. of acetone and 40 ml. of methanol was added 10 g. of cold methyl bromide. The flask was stoppered, clamped and allowed to stand at room temperature for 3 days. The starting material completely dissolved. The solution was concentrated on a steam-bath by a stream of nitrogen giving an oil which crystallized. This was triturated with absolute ether, collected and dried giving 9.9 g. of white crystalline product. Recrystallization from methanol gave 9.85 g. (98.8%), m.p. 191–193°.

Anal. Calcd. for $C_{28}H_{39}BrN_2O$: C, 67.32; H, 7.87; Br, 16.00. Found: C, 67.12; H, 8.09; Br, 16.06.

10-[β-(1-(1-Azaspiro[4.5]decane))-ethyl]-phenothiazine Hydrochloride (XVI).—A mixture of 14.0 g. (0.07 mole) of phenothiazine, 100 ml. of dry toluene and 2.93 g. (0.075 mole) of sodium amide was heated under reflux under nitrogen with vigorous stirring for 2 hours. After cooling, 83.3 ml. (0.075 mole) of a toluene solution of 1-(β-chloroethyl)-1-azaspiro[4.5]decane (see above under preparation of the nitrile) was added dropwise with vigorous stirring during 15 minutes. It was then heated under reflux for 19 hours. The mixture was washed with water and then the toluene solution was shaken with 400 ml. of water containing 15 ml. of concentrated hydrochloric acid. An oil separated which soon crystallized. The solid was collected, washed with water and ether and dried, giving 26.8 g. (91.3%) of tan crystals, m.p. 107–130°. This was recrystallized from water giving 25.7 g. of nearly white crystals, m.p. 120–130° dec. Infrared spectrum indicates it is a hydrate.

Anal. Calcd. for $C_{23}H_{29}ClN_2S \cdot H_2O$: C, 65.93; H, 7.46; N, 6.69; Cl, 8.46; S, 7.65. Found: C, 66.10; H, 7.59; N, 6.47; Cl, 8.54; S, 7.96.

10-[γ-(1-(1-Azaspiro[4.5]decane))-propyl]-2-chlorophenothiazine (XVII).—A mixture of 11.7 g. (0.05 mole) of 2-chlorophenothiazine,[13] 2.06 g. (0.053 mole) of sodium amide and 75 ml. of dry toluene was heated under reflux under nitrogen with vigorous stirring for 2 hours.

A mixture of 13.4 g. (0.053 mole) of 1-(γ-chloropropyl)-1-azaspiro[4.5]decane hydrochloride and dilute sodium hydroxide was extracted with 100 ml. of toluene in four portions. The toluene extracts were washed with a little water and well dried over potassium carbonate.

This toluene solution was added slowly during 10 minutes to the suspension of the sodium salt of chlorophenothiazine with vigorous stirring. The mixture was heated under reflux for 8 hours, cooled, washed twice with water and the washings were extracted with ether. The toluene and ether solutions of the free base were shaken with dilute hydrochloric acid. An oily hydrochloride separated insoluble in both layers. The hydrochloride and aqueous layers were separated, washed with ether and made basic with sodium hydroxide. The free base separated as an oil which soon crystallized. The solid was collected, washed with water and dried giving 19 g. of tan solid, m.p. 108–112°. This was crystallized from 100 ml. of ethyl acetate (with treatment with decolorizing charcoal) giving 15.3 g. (74%) of cream-colored crystals, m.p. 114–116°. A small sample recrystallized from acetone gave crystals with the same color and melting point.

Anal. Calcd. for $C_{24}H_{29}ClN_2S$: C, 69.79; H, 7.08; Cl, 8.58. Found: C, 69.83; H, 7.08; Cl, 8.78.

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(12) B. G. Gokhale, N. L. Pholikae and B. V. Bhide, *J. Univ. Bombay*, **16**, No. 5, 32 (1948); *C. A.*, **43**, 1144 (1949).

(13) P. Charpentier, U. S. Patent 2,645,640 (1953).