

Spirans XX. Synthesis of 8,8-Dialkylazaspiro[4.5]decane and 9,9-Dialkylazaspiro[5.5]undecanes.

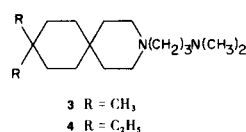
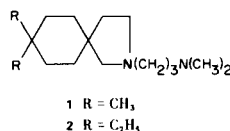
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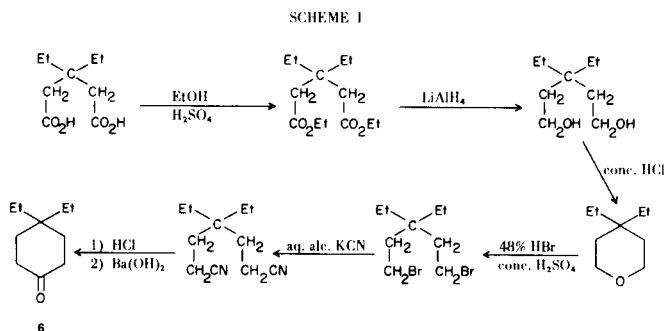
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N-(2-Dimethylaminopropyl)-8,8-dimethyl-2-azaspiro[4.5]decane (**1**), *N*-(2-dimethylamino-propyl)-8,8-diethyl-2-azaspiro[4.5]decane (**2**), *N*-(3-dimethylaminopropyl)-9,9-dimethyl-3-azaspiro[5.5]undecane (**3**), and *N*-(3-dimethylaminopropyl)-9,9-diethyl-3-azaspiro[5.5]undecane (**4**) have been synthesized from 4,4-dimethylcyclohexanone (**5**) and 4,4-diethylcyclohexanone (**6**). Biological evaluation of these amines showed significant inhibition of cancer cell growth in human cancer cells grown in tissue culture.

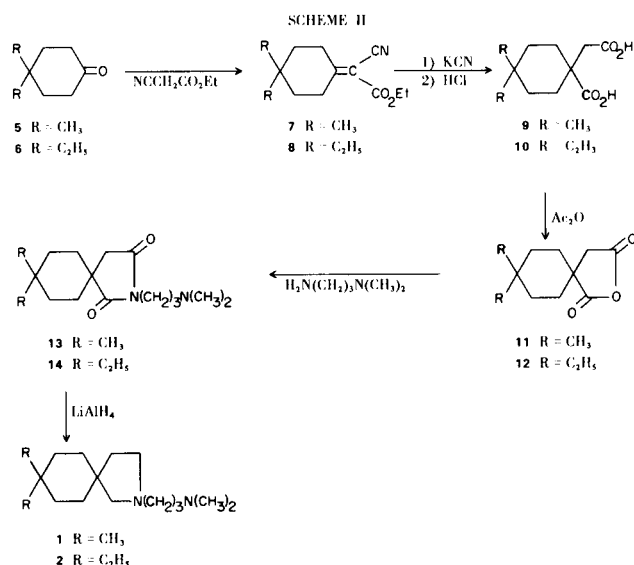
Continuing our efforts to investigate the chemotherapeutic effects of azaspirans (**2**), *gem*-dimethyl (**1** and **3**) and *gem*-diethyl (**2** and **4**) groups have been introduced into the basic azaspirans (**1**) and (**3**) ($R = H$). Since introduction of a single methyl group at these positions had led to a five fold increase of inhibitory action in KB cells and human mammary cancer grown in tissue culture (**2**), further substitution at these positions was attempted.



The starting materials for construction of the spiran ring were 4,4-dimethylcyclohexanone (**5**) and 4,4-diethylcyclohexanone (**6**). Several methods have been employed for the synthesis of 4,4-dimethylcyclohexanone (**5**), (3,4). The method of Bordwell and Wellman (4) which is short and convenient was used. The synthesis of 4,4-diethylcyclohexanone (**6**) has been reported as a four step process by Colonge and Vuillemet (5). 4,4-Diethyl-2-cyclohexenone was prepared by the modified method of Franke and Bueren, (5,6) and reduced to ketone **6**. In addition, an alternate method utilized for **6** is also known in Scheme I.



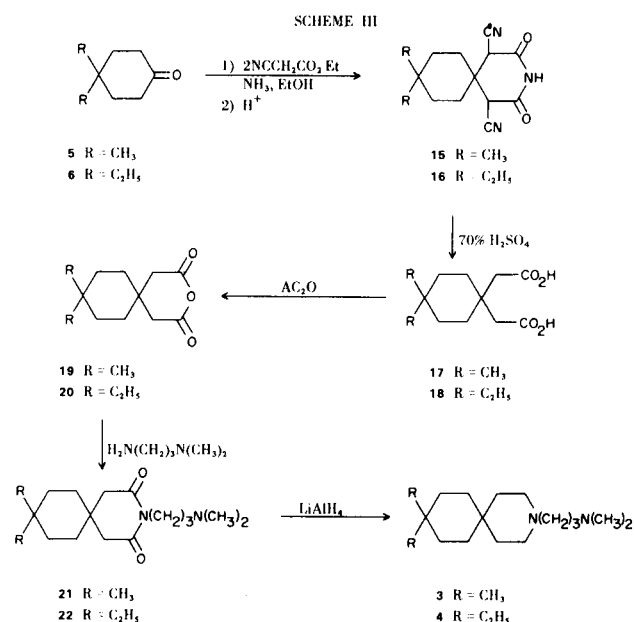
The synthetic approach to aza compounds **1** and **2** is shown in Scheme II. A Cope procedure (7) was used to condense ethyl cyanoacetate with ketones **5** and **6** giving



the unsaturated cyanoesters **7** and **8**. Addition of cyanide followed by hydrolysis gave the diacids **9** and **10** which were converted to their corresponding anhydrides **11** and **12**. The gem-dimethyl group in anhydride **11** exhibited nonequivalence in its pmr spectrum which appeared as two singlets at δ 0.97 and 1.01. Treatment of the anhydrides with 3-dimethylaminopropylamine gave the aminoimides **13** and **14**. As with anhydride **11**, **13** also exhibited nonequivalence of methyl groups. Reduction of the imides with lithium aluminum hydride gave amines **1** and **2** which were characterized as their dihydrochlorides and dimethiodides.

The synthetic route to amines **3** and **4** is shown in Scheme III. The dialkyl ketones **5** and **6** were again used as intermediates. Two moles of ethyl cyanoacetate were condensed with the ketones under the conditions of Guareschi (8). This approach has been widely used in the preparation of *gem*-disubstituted glutaric acids by Thorpe (9) and Vogel (10). Hydrolysis and decarboxylation of imides **15** and **16** gave the diacids **17** and **18** which were converted to the anhydrides **19** and **20**. Treatment of the anhydrides with 3-dimethylaminopropylamine as before gave imides **21** and **22** which were reduced to amines **3** and **4**. As with **1** and **2**, these were characterized as their dihydrochlorides and dimethiodides.

Amines **1** and **3** as their dihydrochloride salts showed acute LD₅₀ in range of 100-125 mg./kg. in rats. When the same compounds were assayed against human cancer cells grown in tissue culture, both **1** and **3** inhibited complete cancer cell growth at a concentration of 1×10^{-5} g./ml. Similar test evaluation for amines **2** and **4** is in progress.



EXPERIMENTAL

All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, New York. Ir spectra were taken on a Perkin-Elmer Model 137 using polystyrene as a calibration. The pmr spectra were obtained on a Varian A-60 spectrometer using TMS as an internal standard; chemical shifts are expressed in parts per million (δ) from the internal standard. Anhydrous sodium sulfate was used as a drying agent.

4,5-Dimethylcyclohexanone (**5**).

This compound was prepared by catalytic hydrogenation of 4,4-dimethyl-2-cyclohexenone as previously described by Bordwell and Wellman (4); ir (Nujol): 5.82 μ .

4,4-Diethylcyclohexanone (**6**).

To a solution of 54.1 g. (0.355 mole) of 4,4-diethyl-2-cyclohexenone (**6**) dissolved in 200 ml. of glacial acetic acid, 0.9 g. of 10% Pd on C was added and the mixture was shaken on a Parr apparatus, the mixture filtered, and the filtrate poured into a mixture of water and ether. The acetic acid was neutralized with solid sodium bicarbonate. The aqueous layer was washed twice with ether, the ether layers combined, dried, and concentrated. The resulting oil was distilled at 74-75° (2.0 mm) to yield 48.5 g. (89%) of the desired ketone [lit. (5) b.p. 104° (18 mm)]; ir (neat): 5.81 μ ; pmr (deuteriochloroform) δ 0.86 (t, 6, J = 7 Hz), 1.10-1.93 (m, 8), and 2.32 (t, 4, J = 7 Hz). The semicarbazone melted at 199-200° [lit. (5) 202°].

Diethyl 3,3-diethylglutarate.

3,3-Diethylglutaric acid (**10**), (100 g., 0.53 mole) was esterified by the method of Vogel (11). The product was distilled at 138° (10 mm) giving 116.8 g. (90%) of ester: ir (neat): 5.73 μ ; pmr (deuteriochloroform) δ 0.85 (t, 6, J = 7 Hz), 1.24 (t, 7, J = 7 Hz), 1.51 (q, 4, J = 7 Hz), 2.43 (s, 4), and 4.13 (q, 4, J = 7 Hz).

3,3-Diethyl-1,5-dihydroxypentane.

To a solution of 13 g. of lithium aluminum hydride in 1 l. of anhydrous ether, a solution of 67 g. (0.274 mole) of diethyl 3,3-diethyl glutarate in 500 ml. of anhydrous ether was added over a period of 1 hour and the mixture was stirred for 24 hours. The reaction mixture was decomposed by the dropwise addition of water, stirred for 1 hour, and filtered. The filtrate was dried and the ether evaporated. The thick oily residue was distilled to give 40.4 g. (91%) of the diol (**12**) b.p. 120-122° (0.4 mm); ir (neat): 2.96 μ ; pmr (deuteriochloroform): δ 0.82 (t, 6, J = 6 Hz), 0.99-1.77 (m, 8), 3.65 (broad t, 4), and 4.19 (broad s, 2).

Anal. Calcd. for C₉H₂₀O₂: C, 67.45; H, 12.58. Found: C, 67.70; H, 12.78.

4,4-Diethyltetrahydropyran.

3,3-Diethyl-1,5-dihydroxypentane, (58.9 g., 0.367 mole) was refluxed with 120 ml. of concentrated hydrochloric acid on a steam bath for 2 hours. The reaction mixture was cooled and poured into an ice-cold mixture of water and ether, neutralized with solid sodium carbonate, the aqueous layer separated, and extracted with small portions of ether. The ether layers were combined and washed with water, saturated salt solution, and dried. The ether was evaporated and the product distilled giving 45.4 g. (98%) of 4,4-diethyltetrahydropyran, b.p. 72-74° (15.5 mm); ir (neat): 8.99 μ ; pmr (deuteriochloroform): δ 0.78 (t, 6, J = 7 Hz), 1.13-1.88 (m, 8), and 3.67 (t, 4, J = 6 Hz).

Anal. Calcd. for $C_9H_{18}O$: C, 76.00; H, 12.78. Found: C, 75.87; H, 12.75.

3,3-Diethyl-1,5-dibromopentane.

To a solution of 44.4 g. (0.312 mole) of 4,4-diethyltetrahydropyran dissolved in 200 ml. of 48% hydrobromic acid was slowly added 100 ml. of concentrated sulfuric acid in small portions with cooling and shaking. The mixture was heated on a steam bath for 22 hours and after cooling was poured into 750 ml. of ice water. The separated oil was extracted with ether and the ether solution was washed with water, saturated salt solution, and dried. After removal of ether, the pale brown residue was distilled at 144° (8.8 mm) to give 73.6 g. (82%) of the dibromide. The product gave a positive test for bromine; pmr (deuteriochloroform): δ 0.82 (t, 6, $J = 6$ Hz), 1.21-1.60 (m, 4), 1.60-2.10 (m, 4), and 3.10-3.60 (m, 4).

Anal. Calcd. for $C_9H_{18}Br_2$: C, 37.79; H, 6.41. Found: C, 37.84; H, 6.31.

3,3-Diethyl-1,5-dicyanopentane.

To a solution of 72.5 g. (0.253 mole) of 3,3-diethyl-1,5-dibromopentane in 500 ml. of ethanol was added a solution of 39.5 g. of potassium cyanide dissolved in 70 ml. of water. The mixture was refluxed for 24 hours and after cooling was poured into 1.5 l. of ice water. The crude product solidified, was filtered, washed with water, pressed and air-dried. The dinitrile was distilled, b.p. $113-117^\circ$ (0.026 mm), 27.1 g. (60%), m.p. $59.5-61^\circ$. Recrystallization from ethyl acetate-ligroin gave the material of m.p. $61.5-62.5^\circ$; ir (Nujol): 4.44μ ; pmr (deuteriochloroform): δ 0.82 (t, 6, $J = 6$ Hz), 1.03-1.40 (m, 4), 1.40-1.86 (m, 4), and 2.03-2.45 (m, 4).

Anal. Calcd. for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18; N, 15.71. Found: C, 74.33; H, 10.48; N, 15.69.

4,4-Diethylpimelic Acid.

To 25.8 g. (0.144 mole) of 3,3-diethyl-1,5-dicyanopentane was added 200 ml. of concentrated hydrochloric acid and the mixture was refluxed for 20 hours. After cooling, the mixture was diluted with 500 ml. of water and filtered. The crude acid was treated with potassium bicarbonate solution, filtered, and acidified with concentrated hydrochloric acid. The acid after drying melted at $126-127^\circ$, 25.3 g. (81%) and after recrystallization from ethyl acetate gave material of m.p. $127-128^\circ$ [lit. (5) 126°]; ir (Nujol): 5.77μ ; pmr (DMSO- d_6): δ 0.72 (broad t, 6), 0.89-1.62 (m, 8), 1.66-2.29 (m, 4), and 12 (s, 2).

Anal. Calcd. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.28; H, 9.54.

4,4-Diethylcyclohexanone (6).

Powdered 4,4-diethylpimelic acid, 25 g. (0.115 mole) was mixed with 4 g. of barium hydroxide. On heating the mixture, some water distilled over the melting point of the acid and the active pyrolysis started at 180° . The pressure was reduced to 250 mm and gradually reduced to 15 mm as the reaction proceeded and all the distillate was collected. The distillate was dissolved in ether, washed with saturated potassium bicarbonate solution, water, and saturated salt solution. The ether was removed after drying and the residue distilled at 74° (2.0 mm) to yield 8.6 g. (48%) of ketone **6**. The ir and pmr spectra were identical with the previously prepared ketone. The semicarbazone melted at $199-200.5^\circ$ and the admixture melting point showed no depression.

Ethyl α -Cyano- α -(4,4-dimethylcyclohexylidene)acetate (7).

A mixture of 21.08 g. (0.167 mole) of **5**, 18.9 g. (0.167 mole)

of ethyl cyanoacetate, 2 g. (0.033 mole) glacial acetic acid, and 1.38 g. (0.0167 mole) ammonium acetate in 50 ml. of dry benzene was refluxed and the water removed with a Dean-Stark tube. After removal of benzene and unreacted material, the product was distilled at $83-86^\circ$ (0.1 mm) giving 22.7 g. (61%) of **7** which solidified, m.p. $53.5-55^\circ$ [lit. (3a) 155° (7 mm), m.p. 50°]; ir (Nujol): $4.46, 5.75$ and 6.23μ ; pmr (deuteriochloroform): δ 1.03 (s, 6), 1.18-1.76 (m, 4), 1.35 (t, 3, $J = 7$ Hz), 2.73 (t, 2, $J = 7$ Hz), 3.04 (t, 2, $J = 7$ Hz), and 4.30 (q, 2, $J = 7$ Hz).

Ethyl α -Cyano- α -(4,4-diethylcyclohexylidene)acetate (8).

A mixture of 17 g. (0.11 mole) of **6**, 11.3 g. (0.1 mole) of ethyl cyanoacetate, 1.2 g. (0.02 mole) glacial acetic acid, and 0.77 g. (0.01 mole) ammonium acetate in 50 ml. of benzene was treated as in the preparation of **7**. The product distilled at b.p. $110-113^\circ$ (0.08 mm), 22.3 g. (81%); ir (neat): $4.47, 5.76$, and 6.24μ ; pmr (deuteriochloroform): δ 0.82 (t, 6, $J = 7$ Hz), 1.33 (t, 3, $J = 7$ Hz), 1.34-2.02 (m, 8), 2.70 (broad t, 2), 3.02 (broad t, 2), and 4.28 (q, 2, $J = 7$ Hz).

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.54; H, 9.56; N, 5.54.

4,4-Dimethylcyclohexane-1-carboxy-1-acetic Acid (9).

To a solution of 19.3 g. (0.0871 mole) of **7** in 72 ml. of alcohol, a solution of 8.6 g. of potassium cyanide dissolved in 20 ml. of water was added and the mixture was stored at room temperature for 2 days. The solvents were removed and the dry salt was refluxed with 190 ml. of concentrated hydrochloric acid for 12 hours. The mixture was diluted with an equal volume of water, cooled, and filtered. The resulting solid was dissolved in a saturated solution of potassium bicarbonate, boiled, and filtered while hot. The filtrate was acidified with concentrated hydrochloric acid with stirring and the diacid was precipitated. On cooling, the acid was filtered, washed with cold water, pressed, and dried, 17.7 g. (95%), m.p. $169-171^\circ$. A portion on recrystallization from benzene-petroleum ether melted at $171-172.5^\circ$ [lit. (3a) 189°]; ir (Nujol): 5.85μ ; pmr (DMSO- d_6): δ 0.88 (s, 6), 1.06-2.18 (m, 8), 2.47 (s, 2), and 12 (s, 2).

4,4-Diethylcyclohexane-1-carboxy-1-acetic Acid (10).

A solution of 20 g. (0.08 mole) of **8** in 130 ml. of alcohol was mixed with 10.4 g. (0.16 mole) of potassium cyanide in 15 ml. of water and treated as in the preparation of **9**, giving 18.8 g. (97%) of **10**, m.p. $150.5-151.5^\circ$; ir (Nujol) 5.85μ ; pmr (DMSO- d_6): δ 0.71 (broad t, 6), 0.91-2.10 (m, 12), 2.46 (s, 2), and 12 (broad s, 2).

Anal. Calcd. for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.39; H, 9.30.

4,4-Dimethylcyclohexane-1-carboxy-1-acetic Acid Anhydride (11).

A mixture of 13.1 g. (0.0611 mole) of diacid **9** and 60 ml. of acetic anhydride was refluxed for 2 hours and the excess acetic anhydride was removed by vacuum distillation. The residue was recrystallized from ligroin, 10.8 g. (90%), m.p. $124-125^\circ$ [lit. (3a) 124°]; ir (Nujol) 5.36 and 5.60μ ; pmr (deuteriochloroform): δ 0.97 (s, 3), 1.01 (s, 3), 1.10-2.40 (m, 8), and 2.80 (s, 2).

4,4-Diethylcyclohexane-1-carboxy-1-acetic Acid Anhydride (12).

Diacid **10**, 10 g. (0.412 mole) was treated as in the preparation of **11**. Distillation at $116-130^\circ$ (0.08 mm) gave 8.4 g. (91%) of **12**, m.p. $92-93^\circ$; ir (Nujol) 5.43 and 5.56μ ; pmr (deuteriochloroform): δ 0.79 (t, 6, $J = 7$ Hz), 0.99-2.09 (m, 12), and 2.81 (s, 2).

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.88; H, 9.29.

N-(2-Dimethylaminopropyl)-8,8-dimethyl-2-azaspiro[4.5]decane-1,3-dione (**13**).

3-Dimethylaminopropylamine (5.6 g.) was added dropwise to 10.2 g. (0.0525 mole) of powdered anhydride **11** and the mixture was heated at 180° for 1 hour to complete the reaction. The reaction mixture was allowed to cool and distilled at $144-148^\circ$ (0.6 mm). The pale yellow solid, 12.3 g. (83%) melted at $59-60^\circ$; *ir* (Nujol): 3.59, 5.62, and $5.84\ \mu$; *pmr* (deuteriochloroform): δ 0.96 (s, 3), 1.0 (s, 3), 1.09-1.90 (m, 10), 2.19 (s, 6), 2.29 (t, 2, $J = 7$ Hz), 2.50 (s, 2), and 3.55 (t, 2, $J = 7$ Hz).

Anal. Calcd. for $C_{16}H_{28}N_2O_2$: C, 68.53; H, 10.06; N, 9.99. Found: C, 68.36; H, 9.87; N, 9.68.

The hydrochloride was prepared by dissolving the imide **13** in absolute alcohol and by adding a saturated solution of absolute alcoholic hydrogen chloride gas to make the solution acidic. Anhydrous ether was slowly added until the solution became turbid. The solution was cooled, filtered, and the white shiny material was dried, m.p. $213.5-215^\circ$. Recrystallization from ethyl acetate-ethanol gave material of m.p. $213.5-214.5^\circ$.

Anal. Calcd. for $C_{16}H_{29}ClN_2O_2$: Cl, 11.19. Found: Cl, 11.34.

The methiodide of the imide **13** was made by adding excess methyl iodide to a solution of the imide dissolved in ethyl acetate. The precipitated solution was cooled, filtered and white crystalline material was dried, m.p. $243-244^\circ$. Recrystallization from ethanol gave material of m.p. $243-243.5^\circ$.

Anal. Calcd. for $C_{17}H_{31}IN_2O_2$: I, 30.00. Found: I, 30.02.

N-(2-Dimethylaminopropyl)-8,8-diethyl-2-azaspiro[4.5]decane-1,3-dione (**14**).

Dimethylaminopropylamine, 3.64 g. (0.0356 mole) was added dropwise with stirring to 8 g. (0.0356 mole) of powdered **12**. The mixture grew warm and was heated on an oil-bath at 180° for 1 hour to complete cyclization. The liquid was cooled and distilled at $143-147^\circ$ (0.11 mm) to give 10 g. (91%) of **14**, m.p. $53-55.5^\circ$ after recrystallization from ligroin; *ir* (Nujol): 3.59, 5.62 and $5.84\ \mu$; *pmr* (deuteriochloroform): δ 0.78 (almost equivalent overlapping t, 6, $J = 7$ Hz), 0.97-2.10 (m, 14), 2.19 (s, 6), 2.28 (t, 2, $J = 7$ Hz), 2.51 (s, 2), and 3.56 (t, 2, $J = 7$ Hz).

Anal. Calcd. for $C_{18}H_{32}N_2O_2$: C, 70.09; H, 10.46; N, 9.08. Found: C, 70.18; H, 10.46; N, 9.01.

N-(2-Dimethylaminopropyl)-8,8-dimethyl-2-azaspiro[4.5]decane (**1**).

To a solution of 5 g. of lithium aluminum hydride in 250 ml. of anhydrous ether was added slowly a solution of 9.5 g. (0.0338 mole) of imide **13** dissolved in 150 ml. of anhydrous ether and the mixture was stirred for 3 hours at room temperature. The reaction mixture was decomposed by the slow addition of 20 ml. of water, allowed to stir for 1 hour, filtered and the white inorganic solid washed thoroughly with anhydrous ether. The ethereal solution was dried, and the solvent removed. The residue was distilled at $69-73^\circ$ (0.05 mm) to yield 6.83 g. (80%) of pale yellow oily **1**; *pmr* (deuteriochloroform): δ 0.9 (s, 6), 1.0-1.91 (m, 12), 2.21 (s, 6), 2.27-2.73 (overlapping t, 6), and 2.34 (s, 2).

Anal. Calcd. for $C_{16}H_{32}N_2$: C, 76.13; H, 12.78; N, 11.10. Found: C, 76.35; H, 12.77; N, 10.97.

The dihydrochloride derivative was prepared by dissolving amine **1** in absolute alcohol and making the solution acidic by adding a saturated solution of alcoholic hydrogen chloride gas. The precipitated white solid was cooled, filtered, and dried, m.p. $304-305^\circ$. Recrystallization from alcohol raised the melting

point to $305-306.5^\circ$.

Anal. Calcd. for $C_{16}H_{34}Cl_2N_2$: Cl, 21.79. Found: Cl, 21.60.

The methiodide derivative was obtained by refluxing amine **1** in absolute alcohol with excess methyl iodide for 2 hours. The mixture was brought to room temperature and sufficient ethyl acetate was added to make the solution turbid. The solution was cooled, filtered, and the white shiny crystalline material was dried, m.p. $273-274.5^\circ$. The methiodide melted at $274-274.5^\circ$ after recrystallization from alcohol.

Anal. Calcd. for $C_{18}H_{38}I_2N_2$: I, 47.32. Found: I, 47.71.

N-(2-Dimethylaminopropyl)-8,8-diethyl-2-azaspiro[4.5]decane (**2**).

To a solution of 2 g. of lithium aluminum hydride in 125 ml. of anhydrous ether, a solution of 9 g. (0.0291 mole) of imide **14** was slowly added with stirring. Using the same procedure used for preparation of **1**, the ether was removed and the pale yellow oil was distilled to give 6.53 g. (80%) of amine **2**, b.p. $105-108^\circ$ (0.03 mm); *pmr* (deuteriochloroform): δ 0.74 (t, 6, $J = 7$ Hz), 1.0-1.86 (m, 16), 2.22 (s, 6), 2.34 (s, 2), and 2.27-2.71 (overlapping t, 6).

Anal. Calcd. for $C_{18}H_{36}N_2$: C, 77.07; H, 12.94; N, 9.99. Found: C, 77.41; H, 12.92; N, 9.90.

Dihydrochloride salt m.p. $297.5-298.3^\circ$.

1,5-Dicyano-9,9-dimethyl-3-azaspiro[5.5]undecane-2,4-dione (**15**).

A mixture of 63 g. (0.5 mole) of **5** and 113.2 g. (1.0 mole) of ethyl cyanoacetate were placed in a 2-l., thick-wall flask and the flask was warmed until the solution became homogeneous then cooled to 0° . To this solution was added 600 ml. of absolute alcohol previously saturated with anhydrous ammonia at 0° . The flask was stoppered, sealed with a tape, and stored at $0-5^\circ$ for 2 days. The precipitated ammonium salt of dicyanoimide was filtered, pressed, and washed twice with anhydrous ether and dried. The dried salt was dissolved in a minimal amount of boiling water, filtered while hot, the warm filtrate acidified with concentrated hydrochloric acid with stirring and allowed to cool. The product was filtered, washed with cold water, pressed, and dried to yield 98.2 g. (76%). A portion on recrystallization from alcohol gave material of m.p. $238.5-239.5^\circ$ [lit. (3a) 230°]; *ir* (Nujol): 3.08, 4.43, and $5.80\ \mu$; *pmr* (DMSO- d_6): δ 0.92 (s, 6), 1.16-1.86 (m, 8), 4.70 (s, 1), and 4.92 (s, 2).

1,5-Dicyano-9,9-diethyl-3-azaspiro[5.5]undecane-2,4-dione (**16**).

A mixture of 33.3 g. (0.216 mole) of **6** and 48.9 g. (0.432 mole) of ethyl cyanoacetate was treated as in the preparation of **15**. The precipitated imide was filtered, washed with water, pressed and dried giving 31.1 g. (50%), m.p. $196-198^\circ$. A portion on recrystallization from alcohol melted at $203-204.5^\circ$; *ir* (Nujol) 3.05, 4.43, and $5.76\ \mu$; *pmr* (DMSO- d_6): δ 0.73 (t, 6, $J = 6.5$ Hz), 0.99-1.96 (m, 12), 4.69 (s, 1), and 4.90 (s, 1).

Anal. Calcd. for $C_{16}H_{21}N_3O_2$: C, 66.88; H, 7.37; N, 14.62. Found: C, 67.11; H, 7.23; N, 14.49.

4,4-Dimethylcyclohexane-1,1-diacetic Acid (**17**).

Powdered **15**, 97.5 g. (0.376 mole), dissolved in 378.2 ml. of concentrated sulfuric acid and was allowed to stand overnight at room temperature. To this clear solution 284 ml. of water to make 70% sulfuric acid was added in portions through the condenser with shaking and the mixture refluxed for 2 days. The reaction mixture was diluted with water, cooled, and filtered. The residue was dissolved in boiling potassium bicarbonate solution, decolorized with charcoal, and filtered while hot. The filtrate was acidified with concentrated hydrochloric acid, cooled overnight, filtered, washed with cold water, pressed, and dried, giving 76.9 g.

(91%) of **17**, m.p. 222.5-224.5°. A portion on recrystallization from alcohol melted at 223-224.5° [lit. (3a) 213-218°]; ir (Nujol): 5.85 μ ; pmr (DMSO- d_6): δ 0.87 (s, 6), 0.99-1.74 (m, 8), 2.42 (s, 4), and 12 (s, 2).

4,4-Diethylcyclohexane-1,1-diacetic Acid (**18**).

Powdered imide **16**, 26.5 g. (0.0922 mole) was dissolved in 150 ml. of concentrated sulfuric acid and treated as in the preparation of **17**. The diacid was filtered, washed with cold water, and dried giving 17.2 g. (73%) of **18**, m.p. 191-192°. Recrystallization from ethyl acetate gave material of m.p. 192.5-193.5°; ir (Nujol) 5.85 μ ; pmr (DMSO- d_6): δ 0.72 (broad t, 6), 0.93-1.75 (m, 12), 2.41 (s, 4), and 12 (s, 2).

Anal. Calcd. for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.44; H, 9.58.

4,4-Dimethylcyclohexane-1,1-diacetic Acid Anhydride (**19**).

A mixture of 20 g. (0.0876 mole) of diacid **17** and 100 ml. of acetic anhydride was refluxed for 2.5 hours and the clear solution was cooled. The excess acetic anhydride was removed and the product was distilled at 114-120° (0.05 mm) to yield a white solid, 17.35 g. (95%), m.p. 86-87°. Recrystallization from ligroin gave material of m.p. 88-89° [lit. (3a) 86°]; ir (Nujol): 5.46 and 5.61 μ ; pmr (deuteriochloroform): δ 0.93 (s, 6), 1.40 (broad s, 8), and 2.65 (s, 4).

4,4-Diethylcyclohexane-1,1-diacetic Acid Anhydride (**20**).

Diacid **18**, 16.6 g. (0.0647 mole) was refluxed with 83 ml. of acetic anhydride as in the preparation of **19** to give 14.1 g. (91%) of **20**, b.p. 136-140° (0.13 mm); m.p. 66-67°.

Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.26; H, 9.25.

N-(3-Dimethylaminopropyl)-9,9-dimethyl-3-azaspiro[5.5]undecane-2,4-dione (**21**).

Powdered anhydride **19**, 12.62 g. (0.06 mole) was treated dropwise with 6.2 g. of 3-dimethylaminopropylamine as in the preparation of **13**. The product was distilled at 141-143° (0.1 mm) giving a pale yellow solid **21**, 15.4 g. (88%), m.p. 43.5-45°; ir (Nujol): 3.59, 5.75, and 5.95 μ ; pmr (deuteriochloroform): δ 0.93 (s, 6), 1.36 (broad s, 8), 1.61-1.88 (m, 2), 2.20 (s, 6), 2.30 (t, 2, $J = 7$ Hz), 2.55 (s, 4), and 3.81 (t, 2, $J = 7$ Hz).

Anal. Calcd. for $C_{17}H_{30}N_2O_2$: C, 69.35; H, 10.27; N, 9.51. Found: C, 69.53; H, 9.96; N, 9.84.

Hydrochloride from alcohol, m.p. 189-190.5°.

Anal. Calcd. for $C_{17}H_{31}ClN_2O_2$: Cl, 10.71. Found: Cl, 10.79.

Methiodide from alcohol, m.p. 283-284.5°.

Anal. Calcd. for $C_{18}H_{33}IN_2O_2$: I, 29.08. Found: I, 28.87.

N-(3-Dimethylaminopropyl)-9,9-diethyl-3-azaspiro[5.5]undecane-2,4-dione (**22**).

Powdered anhydride **20**, 12 g. (0.0503 mole) was treated with 5.3 g. of 3-dimethylaminopropylamine and heated at 180° for 1 hour. The cyclized product was cooled and distilled at 147-155° (0.035 mm) to give 14.6 g. (90%) of **22**.

Anal. Calcd. for $C_{19}H_{34}N_2O_2$: C, 70.76; H, 10.63; N, 8.69.

Found: C, 71.02; H, 10.74; N, 8.65.

N-(3-Dimethylaminopropyl)-9,9-dimethyl-3-azaspiro[5.5]undecane (**3**).

A solution of 15 g. (0.0509 mole) of imide **21** was reduced with lithium aluminum hydride (6.3 g.) as in the preparation of **1**; yield 12.5 g. (92%) of amine **3**, b.p. 93-94° (0.02 mm); pmr (deuteriochloroform): δ 0.90 (s, 6), 1.03-1.70 (m, 14), 2.22 (s, 6), and 2.26-2.53 (m, 8).

Anal. Calcd. for $C_{17}H_{34}N_2$: C, 76.63; H, 12.86; N, 10.51. Found: C, 76.82; H, 12.69; N, 10.79.

Dihydrochloride from ethanol, m.p. 334-335°.

Anal. Calcd. for $C_{17}H_{36}Cl_2N_2$: Cl, 20.89. Found: Cl, 20.43. Dimethiodide from ethanol, m.p. 294-295°.

Anal. Calcd. for $C_{19}H_{40}I_2N_2$: I, 46.11. Found: I, 45.91.

N-(3-Dimethylaminopropyl)-9,9-diethyl-3-azaspiro[5.5]undecane (**4**).

A solution of 13.7 g. (0.0424 mole) of imide **22** dissolved in anhydrous ether was reduced with lithium aluminum hydride as in the preparation of **3**. Distillation gave 11.62 g. (93%) of amine **4**, b.p. 114° (0.035 mm); pmr (deuteriochloroform): δ 0.74 (t, 6, $J = 7$ Hz), 0.97-1.91 (m, 18), 2.21 (broad s, 6), and 2.25-2.56 (m, 8).

Anal. Calcd. for $C_{19}H_{38}N_2$: C, 77.48; H, 13.01; N, 9.51. Found: C, 77.78; H, 13.08; N, 9.32.

Dihydrochloride, m.p. 306-307°.

Anal. Calcd. for $C_{19}H_{40}Cl_2N_2$: Cl, 19.30. Found: Cl, 19.38.

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