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## Reactions of 14-Hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione and Related Compounds. II

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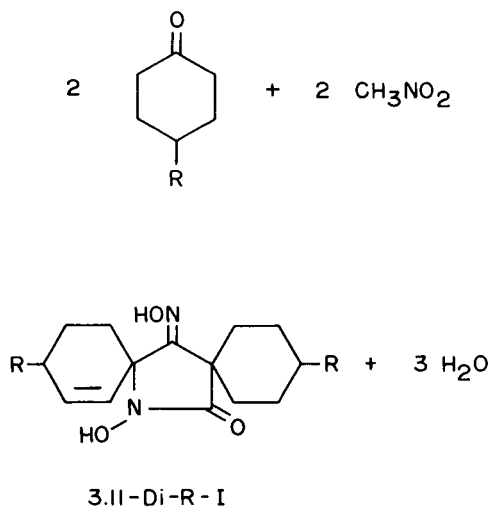
When 3,11-diethyl- and 3,11-di-*n*-propyl-14-hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione (E-IV and *n*-Pr-IV) are heated with polyphosphoric acid at 55-65°, the 14-hydroxyl group cyclizes at the 11-carbon to form E-VI and *n*-Pr-VI, the structures of which have been established. Compounds P-IV, *i*-Pr-IV and *t*-B-IV do not cyclize under these conditions.

The Beckmann rearrangement of 12-hydroxy-12-azadispiro[4.1.4.2]tridec-8-ene-6,13-dione-6-oxime (P-I) with polyphosphoric acid at 40-50° formed only the normal product, P-II, which could not be cyclized.

Compound P-IV was the only ketone of this series which would add hydrogen cyanide to form a cyanohydrin.

Some unexpected reactions of 3,11-dimethyl-14-hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione (M-IV), its 7-oxime (M-I) and compounds obtained from them (2) led us to extend our study to other homologs of these ring systems.

The fact that neither *i*-Pr-IV nor *t*-B-IV would cyclize under the conditions for the cyclization of M-IV to form M-VI suggested that perhaps the size of the radical inhibited cyclization. To test this possibility, E-I and *n*-Pr-I were prepared by the piperazine catalyzed condensation of the corresponding 4-alkylcyclohexanones with nitromethane.



Hydrolysis of their oxime groups with concentrated hydrochloric acid in 1-butanol gave E-IV and *n*-Pr-IV. The *i*-Pr-I and *t*-B-I were best hydrolyzed with concentrated sulfuric acid in 1-butanol.

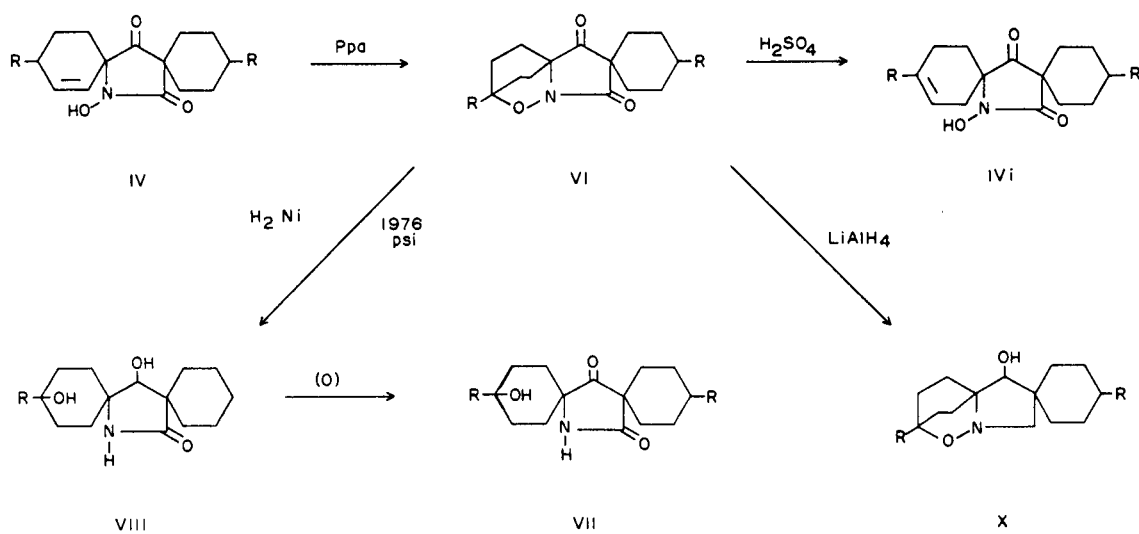
On one occasion, *i*-Pr-IV was obtained in two forms, one m.p. 246-248° dec. and the other m.p. 200-202° dec. Their infrared spectra in Nujol differed in the finger print region, but their n.m.r. spectra were identical, indicating that they are dimorphic forms.

E-IV and *n*-Pr-IV were cyclized by heating with polyphosphoric acid at 65-70° for approximately 20 hours to give E-VI (50%) and *n*-Pr-VI (40.8%), as compared with a 67% yield of M-VI under these same conditions.

Some reactions of E-VI and *n*-Pr-VI which agree with their structures are shown in Chart I. High pressure hydrogenation gave the diols E-VIII and *n*-Pr-VIII by reduction of the ketone and hydrogenolysis of the nitrogen-oxygen bond (3). When these diols reacted with excess potassium dichromate, only one of the alcohol groups was oxidized to form E-VII and *n*-Pr-VII. The infrared spectra of these ketones show 5-membered ring ketone absorption at around 1750  $\text{cm}^{-1}$ , OH and NH absorption between 3010 and 3510  $\text{cm}^{-1}$ . Thus one alcohol group in the diols VIII must be secondary and the other tertiary, and the latter must be on the 11-carbon.

This is confirmed by the n.m.r. spectra of these cyclized products. These spectra of E-VI and *n*-Pr-VI show no signal at 4.8 p.p.m., the region for a methinyl proton attached to the carbon holding the -O-N- linkage. Therefore, cyclization must have occurred at the 11-carbon since only in this

CHART I



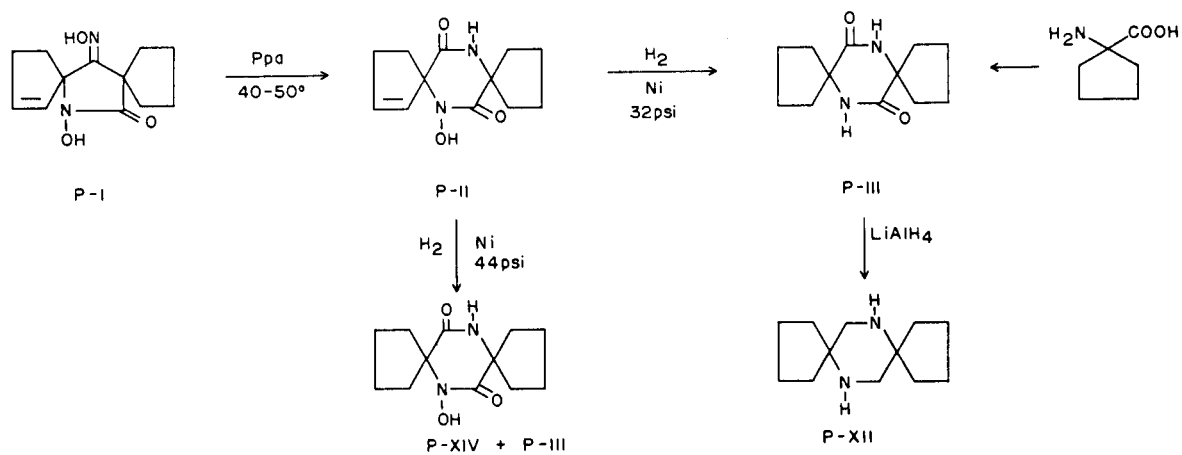
R =  $C_2H_5$ : E-IV, E-IVi, E-VI, E-VIII, E-X

R =  $n-C_3H_7$ : n-Pr-IV, n-Pr-i, n-Pr-VI, n-Pr-VII, n-Pr-VIII

R =  $i-C_3H_7$ : i-Pr-IV      R =  $t-C_4H_9$ : t-B-IV

CHART II

THE BECKMANN REARRANGEMENT



position would one observe no methinyl peak in the n.m.r. spectrum.

The fact that *n*-Pr-IV was converted to *n*-Pr-VI in 63% yield as compared with no cyclization of *i*-Pr-IV or *t*-B-IV suggests that the more bulky radicals inhibit cyclization.

Hydrolysis of E-VI and *n*-Pr-VI with 30% aqueous sulfuric acid gave E-IVi and *n*-Pr-IVi respectively. The infrared spectra of these compounds, which are double bond isomers of E-IV and *n*-Pr-IV, are very similar to those of the compounds IV and both gave a positive ferric chloride test.

The structures of E-IVi and *n*-Pr-IVi were confirmed by their n.m.r. spectra, which show only one vinyl proton at 5.32 p.p.m. The spectra of E-IV and *n*-Pr-IV show two vinyl protons at 5.30 p.p.m. and 6.11 p.p.m.

Reduction of E-VI and *n*-Pr-VI with lithium aluminum hydride gave the alcohols E-X and *n*-Pr-X. The n.m.r. spectrum of these compounds is consistent with this structure since they show a singlet (partly hidden by the alcohol proton) at 3.25 p.p.m. due to the methinyl hydrogen on the alcohol carbon and another singlet at 0.85 p.p.m. due to the two hydrogens on the carbon adjacent to the nitrogen.

In a possible mechanism (4) for the formation of the compounds VI, the first step would be the protonation of the double bond to form a secondary

carbonium ion of the 10-carbon. This ion could rearrange by a 1-2 hydride shift to give a tertiary carbonium ion on the 11-carbon. The boat conformation of this tertiary ion, which would be in equilibrium with the chair conformer, is in an ideal position to undergo irreversible cyclization through nucleophilic attack by the hydroxamic acid group to form the compounds VI.

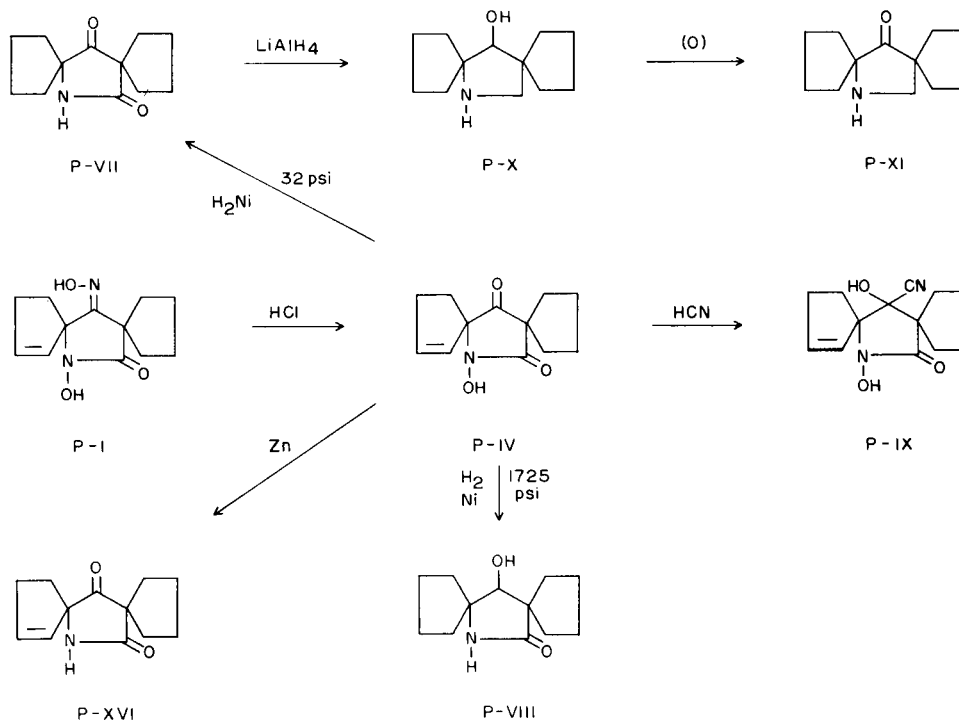
The reactions of these compounds were not extended beyond those shown on the chart, when it appeared likely that they would follow the pattern of the M-series of compounds (2).

A more interesting ring system is that of 12-hydroxy-12-azadispiro[4.1.4.2]tridec-8-ene-6,13-dione (P-IV) and its 6-oxime (P-I).

All efforts to bring about the cyclization of P-IV failed. With polyphosphoric acid at 65-70° or 80-85° only recovered starting material and tar were isolated from the reaction mixture and at 95-110° the only product was tar.

Only the normal rearrangement product, P-II, 13-hydroxy-6,13-diazadispiro[4.2.4.2]tetradecene-7,14-dione (Chart II) was obtained when P-I was heated with polyphosphoric acid at 40-50°. Compound P-II was hydrogenated to P-III, the structure of which was established by thermal cyclization of 1-aminocyclopentanecarboxylic acid. The infrared spectra of the two samples of P-III were identical.

CHART III



Reduction of P-III with lithium aluminum hydride yielded the piperazine, P-XII.

In one hydrogenation of P-II, only the olefinic double bond was reduced, to form the saturated cyclic hydroxamic acid, P-XIV. Compound M-II could be cyclized (2), but this was not possible with P-II.

The structure proof synthesis of P-III establishes the stereochemistry of the oxime hydroxyl of P-I as *syn* with respect to the cyclopentene ring.

As a model experiment for the synthesis of P-III, 1-aminohexanoic acid was thermally cyclized to form 3,6-di-*n*-butyl-2,5-piperazinedione. This compound was then reduced with lithium aluminum hydride to 2,5-di-*n*-butylpiperazine. Piperazines have been synthesized by the high pressure hydrogenation of piperazinediones over copper chromium oxide or with sodium in 1-butanol (low yield) (5), but the lithium aluminum hydride reduction is far more convenient.

Compound P-IV added hydrogen cyanide to form a cyanohydrin, P-IX. The infrared spectrum of this compound showed broad OH absorption at 3400 and 3060, nitrile absorption at 2250 and amide carbonyl at 1630  $\text{cm}^{-1}$ . All attempts to hydrolyze P-IX resulted in nearly quantitative loss of hydrogen cyanide to regenerate P-IV.

In general, the other reactions of P-IV and the compounds obtained from it (Chart III) were analogous to those of the M-series. The notable exceptions were the failure of P-IV and P-II to cyclize.

#### EXPERIMENTAL

All melting points were taken in a open capillary tube in a metal block and are corrected. For compounds which melted with decomposition, the block was heated to within 20° of the melting point before inserting the tube. The microanalyses were performed at the Weiler-Strauss Laboratories, Oxford, England. Unless otherwise stated, the drying agent for organic solutions was anhydrous magnesium sulfate, and the petroleum ether had a b.p. of 60-70°.

Unless otherwise specified, the infrared spectra were determined in Nujol mulls with a Perkin-Elmer 237B spectrophotometer. The n.m.r. spectra were determined with a Varian A-60 spectrometer. The Preparation of the Compounds I.

Compounds P-I, *i*-Pr-I and *t*-B-I were prepared as previously described (6). The E-I and *n*-Pr-I have not been reported.

3,11-Diethyl-14-hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione-7-oxime (E-I).

In a round-bottom flask fitted with a Dean and Stark trap were placed 100 g. (0.8 mole) of 4-ethylcyclohexanone (prepared by the dichromate oxidation of 4-ethylcyclohexanol) 58.3 g. (0.95 mole) of nitromethane, 68.2 g. (0.79 mole) of piperazine and 150 ml. of benzene. After the solution had refluxed for 19 hours the material which had separated was filtered while the mixture was still hot, washed with benzene and with ether, then triturated with warm hydrochloric acid to remove any catalyst. The white solid, (47.4 g., 37%) m.p. 272-276° dec., was recrystallized from benzene to yield E-I as short white needles, m.p. 274-276° dec.

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{29}\text{N}_2\text{O}_3$ : C, 67.47; H, 8.81; N, 8.47. Found: C, 67.53; H, 8.99; N, 8.60.

3,11-Di-*n*-propyl-14-hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione-7-oxime (*n*-Pr-I).

4-*n*-Propylcyclohexanone (prepared by the dichromate oxidation of 4-*n*-propylcyclohexanol) (40 g., 0.28 mole), 20.8 g. (0.34 mole) of nitromethane, 13.0 g. of piperazine and 75 ml. of benzene were refluxed for 23 hours. The solid which separated was collected on a filter, washed with hot benzene, and triturated with hydrochloric acid to yield 14.4 g. (29%) of a white powder, m.p. 270-274° dec. Recrystallization from methanol gave *n*-Pr-I, m.p. 270-271° dec.

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{32}\text{N}_2\text{O}_3$ : C, 68.93; H, 9.26; N, 8.04. Found: C, 69.05; H, 9.20; N, 8.24.

The Preparation of the Compounds IV.

Compound P-IV has been reported previously (7) but is more conveniently prepared by hydrolysis of P-I with hydrochloric acid in 1-butanol.

12-Hydroxy-12-azadispiro[4.1.4.2]tridec-8-ene-6,13-dione (P-IV).

Compound P-I (20.0 g.), 500 ml. of concentrated hydrochloric acid and 100 ml. of 1-butanol were refluxed for 1.5 hours. The solution was concentrated by distillation until most of the 1-butanol had been removed. The hot solution remaining in the distilling flask was then filtered to remove some tarry material and the crystals which separated from the cooled filtrate were collected and dried in an oven at 100° to yield 14.8 g. (79%) of P-IV, m.p. 158-160°, reported (8) 157-158°; infrared bands at 3050, 2720, 1750, 1665, and 1600  $\text{cm}^{-1}$ .

3,11-Diethyl-14-hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione (E-IV).

A solution of 11.0 g. (0.03 mole) of E-I in 250 ml. of concentrated hydrochloric acid and 200 ml. of 1-butanol was refluxed for 2 hours. The solution was concentrated by distillation until a solid began to separate, then cooled to room temperature, and diluted with water. The solid was collected on a filter and recrystallized from methanol to yield 7.89 g. (76%) of E-IV, m.p. 157-159°. Recrystallization from methanol gave white crystals, m.p. 164-165°; infrared bands at 3110, 3060, 1760, 1690 and 1650  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{27}\text{NO}_3$ : C, 70.79; H, 8.91; N, 4.59. Found: C, 70.84; H, 8.61; N, 4.90.

3,11-Di-*n*-propyl-14-hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione (*n*-Pr-IV).

A mixture of 16 g. of *n*-Pr-I, 300 ml. of concentrated hydrochloric acid and 250 ml. of 1-butanol was refluxed for 1.5 hours. The solution was concentrated until 320 ml. of distillate had been removed, then diluted with 200 ml. of water and cooled. The separated solid was collected on a filter and crystallized from aqueous methanol to yield 9.7 g. (63%) of *n*-Pr-IV, m.p. 160-162°, which after recrystallization from aqueous methanol melted at 163-164°; infrared bands at 3050, 3000, 1760, 1680 and 1640  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{31}\text{NO}_3$ : C, 72.03; H, 9.37; N, 4.20. Found: C, 72.08; H, 9.45; N, 3.95.

3,11-Di-isopropyl-14-hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione (*i*-Pr-IV).

A mixture of 13 g. of *i*-Pr-I, 400 ml. of 1-butanol and 50 ml. of concentrated sulfuric acid was refluxed for 3 hours then concentrated by distilling off the 1-butanol to a volume of about 100 ml. After cooling the solution in a refrigerator, the separated crystals were collected on a filter, washed with water, dried and crystallized once from methanol to yield 8.05 g. (65%) of white needles, m.p. 246-248° dec. Two more recrystallizations gave *i*-Pr-IV, m.p. 246-248° dec.; infrared bands at 3050, 3000, 1750, 1670 and 1640  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{31}\text{NO}_3$ : C, 72.03; H, 9.37; N, 4.20. Found: C, 72.11; H, 9.39; N, 3.91.

In another experiment the 1-butanol filtrate from the *i*-Pr-IV was concentrated until most of the alcohol had been removed and an oil began to separate. After cooling to room temperature, the oil solidified, the solid was collected on a filter, dried and recrystallized from benzene-petroleum ether to yield 0.49 g. (5%) of *i*-Pr-IV, m.p. 190-194° dec. Two recrystallizations gave white crystals, m.p. 200-202° dec.; infrared bands at 3050, 3000, 2660, 1750, 1680 and 1630  $\text{cm}^{-1}$ . The n.m.r. spectra in deuteriochloroform of this sample and the sample m.p. 246-248° dec. were identical.

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{31}\text{NO}_3$ : C, 72.03; H, 9.37; N, 4.20. Found: C, 71.86; H, 9.19; N, 4.43.

3,11-Di-*t*-butyl-14-hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione (*t*-B-IV).

A mixture of 5 g. of *t*-B-I, 300 ml. of 1-butanol and 50 ml. of concentrated sulfuric acid was refluxed for 2 hours. The solution

was cooled in the refrigerator and the white crystals (4.33 g.) were filtered and dried. Addition of water to the filtrate yielded an additional 0.32 g. of material, making a total of 4.65 g. (83%) of *t*-B-IV, m.p. 286-289° after crystallization from ethanol; infrared bands at 3090, 1760 and 1670  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{22}\text{H}_{35}\text{NO}_3$ : C, 73.09; H, 9.76; N, 3.87. Found: C, 73.09; H, 9.54; N, 4.11.

2',4-Diethyl-3',4'-dihydrospiro[cyclohexane-1,6'(7'H)-[5H-2,4-a]ethano-(2H)pyrrolo[1,2-b][1,2]oxazine]-5',7'-dione (E-VI).

A mixture of 4 g. (0.01 mole) of E-IV and 80 g. of polyphosphoric acid was heated and stirred at 65-70° for 16 hours. After cooling in an ice bath, the polyphosphoric acid was hydrolyzed with ice and the mixture was extracted with chloroform. The chloroform layer was extracted with 20% sodium hydroxide and washed with water, the solution was dried and the solvent evaporated. The residue was crystallized from aqueous ethanol to give 2.0 g. of material, m.p. 168-172°. Recrystallization from petroleum ether yielded E-VI as white plates, m.p. 179-181°; infrared bands at 1760 and 1675  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{27}\text{NO}_3$ : C, 70.79; H, 8.91; N, 4.59. Found: C, 71.09; H, 9.17; N, 4.53.

2',4-Di-*n*-propyl-3',4'-dihydrospiro[cyclohexane-1,6'(7'H)-[5H-2,4-a]ethano-(2H)pyrrolo[1,2-b][1,2]oxazine]-5',7'-dione (*n*-Pr-VI).

A mixture of 5 g. of *n*-Pr-IV and 100 g. of polyphosphoric acid, heated and extracted as described above, yielded a crude product after evaporation of the chloroform, which was dissolved in hot benzene and petroleum ether (b.p. 30-60°) added until the solution became cloudy. After cooling to room temperature, 2.06 g. of pale yellow crystals separated. Recrystallization from petroleum ether gave *n*-Pr-VI as white crystals, m.p. 197-198°; infrared bands at 1760 and 1675  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{31}\text{NO}_3$ : C, 72.03; H, 9.37; N, 4.20. Found: C, 71.75; H, 9.51; N, 4.37.

Hydrogenation of 2',4-Diethyl-3',4'-dihydrospiro[cyclohexane-1,6'(7'H)-[5H-2,4-a]ethano-(2H)pyrrolo[1,2-b][1,2]oxazine]-5',7'-dione (E-VI).

All of the catalytic hydrogenations were carried out in conventional equipment for either high or low pressure reactions. After the mixture was removed from the liner, the catalyst was separated by filtration from the solvent, heated if necessary, and the filtrate was evaporated, leaving a residue which was purified by crystallization from a suitable solvent.

A suspension of 4.0 g. of E-VI in 150 ml. of ethanol was hydrogenated over 1.0 g. of Raney nickel at an initial pressure of 1975 psi and a final temperature of 130°. The crude product was triturated with hot benzene and filtered. The white solid (3 g., 75%), m.p. 199-201°, was recrystallized from aqueous ethanol to give E-VIII as white needles, m.p. 206-207°; infrared bands at 3310, 3240, and 1675  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{31}\text{NO}_3$ : C, 69.86; H, 10.10; N, 4.53. Found: C, 70.02; H, 9.85; N, 4.82.

Hydrogenation of 2',4-Di-*n*-propyl-3',4'-dihydrospiro[cyclohexane-1,6'(7'H)-[5H-2,4-a]ethano-(2H)pyrrolo[1,2-b][1,2]oxazine]-5',7'-dione (*n*-Pr-VI).

A suspension of 3 g. of *n*-Pr-VI in 150 ml. of ethanol was hydrogenated over 0.5 g. of Raney nickel at an initial pressure of 2150 psi at room temperature and a final temperature of 130°. The catalyst was removed by filtration of the cold solution and washed with hot ethanol. The residue from the evaporation of the combined filtrates was triturated with hot benzene and filtered. The solid was crystallized from aqueous methanol to give 2.09 g. (69%) of white needles, m.p. 199-201°, which on further recrystallization gave *n*-Pr-VIII, m.p. 201-203°; infrared bands at 3380, 3310, 1680  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{35}\text{NO}_3$ : C, 71.17; H, 10.45; N, 4.15. Found: C, 70.68; H, 10.47; N, 4.03.

Hydrolysis of 2',4-Diethyl-3',4'-dihydrospiro[cyclohexane-1,6'(7'H)-[5H-2,4-a]ethano-(2H)pyrrolo[1,2-b][1,2]oxazine]-5',7'-dione (E-VI).

A mixture of 5 g. of E-VI, 150 ml. of concentrated sulfuric acid and 350 ml. of water was stirred and refluxed for 3 hours. The mixture was cooled to room temperature, the separated solid was collected on a filter and recrystallized from methanol to yield 3.39 g. (68%) of E-IVI, m.p. 201-203°, which gave a purple color with ferric chloride; infrared bands at 3100, 2730, 1760, 1680, and 1630  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{27}\text{NO}_3$ : C, 70.79; H, 8.91; N, 4.59. Found: C, 70.88; H, 8.86; N, 4.36.

Lithium Aluminum Hydride Reduction of 2',4-Diethyl-3',4'-dihydrospiro[cyclohexane-1,6'(7'H)-[5H-2,4-a]ethano-(2H)pyrrolo[1,2-b][1,2]oxazine]-5',7'-dione (E-VI).

A suspension of 4.0 g. of E-VI in 150 ml. of dry ether was added to a stirred suspension of 2.0 g. of lithium aluminum hydride in 50 ml. of dry ether. After the mixture had stirred and refluxed for 48 hours the excess lithium aluminum hydride was decomposed with 20% aqueous potassium hydroxide solution. The material was filtered and the coagulated white precipitate was extracted with ether. The combined ether filtrates were evaporated at aspirator pressure, leaving 3.17 g. (83%) of white solid, m.p. 121-123°. Recrystallization from aqueous methanol gave E-X, m.p. 126-128°; infrared band at 3200  $\text{cm}^{-1}$  (broad and diffuse).

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{31}\text{NO}_2$ : C, 73.67; H, 10.65; N, 4.77. Found: C, 73.85; H, 10.55; N, 5.06.

Oxidation of 3,11-Diethyl-7,11-dihydroxy-14-azadispiro[5.1.5.2]-pentadec-9-ene-15-one (E-VIII).

To a solution of 1 g. of E-VIII in 30 ml. of glacial acetic acid was added dropwise and with stirring, a solution of 0.96 g. of potassium dichromate and 0.95 g. of concentrated sulfuric acid in 7.8 ml. of water. The resulting solution was kept overnight, then diluted with water and extracted three times with ether. The combined ether extracts were washed with 5% sodium hydroxide solution, dried, and evaporated to dryness. The residue was recrystallized from aqueous methanol to yield 0.78 g. (78%) of E-VII, m.p. 221-222°; infrared bands at 3460, 3290, 3160, 3060, 1750 and 1675  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{29}\text{NO}_3$ : C, 70.32; H, 9.51; N, 4.56. Found: C, 70.56; H, 9.71; N, 4.50.

Oxidation of 3,11-Di-*n*-propyl-7,11-dihydroxy-14-azadispiro[5.1.5.2]-pentadec-9-ene-15-one (*n*-Pr-VIII).

To a solution of 1.0 g. of *n*-Pr-VIII in 30 ml. of glacial acetic acid was added dropwise with stirring a solution of 1.0 g. of potassium dichromate and 1 g. of concentrated sulfuric acid in 10 ml. of water as described above. Evaporation of the combined ether extracts yielded 0.90 g. (91%) of *n*-Pr-VII, m.p. 216-217°; infrared bands at 3620, 3520, 3210, 3100, 1760 and 1690  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{33}\text{NO}_3$ : C, 71.60; H, 9.92; N, 4.18. Found: C, 71.59; H, 9.82; N, 4.39.

Hydrolysis of 2',4-Di-*n*-propyl-3',4'-dihydrospiro[cyclohexane-1,6'(7'H)-[5H-2,4-a]ethano-(2H)pyrrolo[1,2-b][1,2]oxazine]-5',7'-dione (*n*-Pr-VI).

A mixture of 2.0 g. of *n*-Pr-VI, 60 ml. of concentrated sulfuric acid and 140 ml. of water was stirred and refluxed for 3.5 hours then cooled to room temperature and filtered. The solid was washed with water and recrystallized from aqueous methanol to yield 1.24 g. (62%) of *n*-Pr-IVI, m.p. 154-155°, which gave a purple color with ferric chloride; infrared bands at 3100, 2630, 1770, 1690 and 1650  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{31}\text{NO}_3$ : C, 72.03; H, 9.37; N, 4.20. Found: C, 72.20; H, 9.16; N, 4.25.

Beckmann Rearrangement of 12-Hydroxy-12-azadispiro[4.1.4.2]tridec-8-ene-6,13-dione-6-oxime (P-I).

A mixture of 10.0 g. of P-I and 200 g. of polyphosphoric acid was heated with stirring at 40-50° for 24 hours. The resulting cooled solution was stirred with cold water until the polyphosphoric acid had dissolved. The mixture was extracted with 500 ml. of chloroform and the chloroform extract washed with water, then with 20% sodium hydroxide and again with water. The combined aqueous extracts were cooled in an ice bath and acidified to litmus with concentrated hydrochloric acid, then extracted with chloroform. The chloroform extracts were dried and the solvent evaporated at aspirator pressure, leaving 5.10 g. (51%) of a light yellow solid, m.p. 264-268°, which gave a wine red color with ferric chloride solution. Three recrystallizations from methanol yielded P-II as colorless needles, m.p. 268-270°; infrared bands at 3170, 3130, 1675 and 1629  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_3$ : C, 61.00; H, 6.83; N, 11.86. Found: C, 60.69; H, 7.05; N, 12.22.

Hydrogenation of 12-Hydroxy-6,13-diazadispiro[4.2.4.2]tetradecene-7,14-dione (P-II).

A suspension of 2.0 g. of P-II and 0.5 g. of Raney nickel in 100 ml. of absolute ethanol was shaken with hydrogen at 32 psi at room temperature for 19 hours. The mixture was filtered through Filter Cell and the ethanol evaporated, leaving only a trace of solid. The combined catalyst and Filter Cell were extracted in a Soxhlet extractor with 250 ml. of benzene for 3 days. Filtration of the benzene mixture

yielded 1.18 g. (63%) of white crystals, m.p. 300°, which gave no color with ferric chloride. Two recrystallizations from dimethylformamide yielded white crystals of P-III, m.p. 388-390° in a block preheated to 370°; infrared bands at 3260, 3150, 3010, 1660  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_2$ : C, 64.84; H, 8.16; N, 12.60. Found: C, 64.85; H, 8.21; N, 12.42.

In another experiment, hydrogenation of 8.0 g. of P-II in 200 ml. of ethanol with 0.5 g. of Raney nickel at 44 psi for 29 hours yielded 1.03 g. (14%) of P-III isolated as described above. Evaporation of the ethanol filtrate yielded 3.35 g. (42%) of a different white solid, m.p. 258-262°, which gave a purple color with ferric chloride. Three recrystallizations from methanol yielded white crystals of P-XIV, m.p. 261-262°; infrared bands at 3190, 1670 and 1640  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_2$ : C, 60.48; H, 7.61; N, 11.76. Found: C, 60.65; H, 7.74; N, 11.72.

#### Synthesis of 6,13-Diazadispiro[4.2.4.2]tetradecane-7,14-dione (P-III).

The procedure is an adaptation of the synthesis of 3,3,6,6-tetra-methyl-2,5-piperazinedione from  $\alpha$ -aminoisobutyric acid (5). A solution of 10 g. of 1-aminocyclopentanecarboxylic acid in 100 ml. of diethylene glycol was refluxed in a 200 ml. long-neck, round-bottom flask for 4 hours. During this time the solution turned dark brown. After cooling to room temperature, the precipitated solid was collected on a filter and washed with methanol to give 0.29 g. (3%) of a white solid. Two crystallizations from dimethylformamide yielded P-III as white plates, m.p. 388-390°, which did not depress the melting point of P-III prepared by hydrogenation of P-II. The infrared spectra of the two samples were identical.

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_2$ : C, 64.84; H, 8.16; N, 12.60. Found: C, 64.67; H, 8.24; N, 12.82.

#### Lithium Aluminum Hydride Reduction of 6,13-Diazadispiro[4.2.4.2]tetradecane-7,14-dione (P-III).

A suspension of 2.80 g. of P-III in 300 ml. of anhydrous tetrahydrofuran was added to a stirred suspension of 2.6 g. of lithium aluminum hydride in 100 ml. of THF. After stirring and refluxing for 24 hours, the excess hydride was destroyed with 30% aqueous potassium hydroxide. The mixture was filtered and the coagulated white precipitate was extracted with hot tetrahydrofuran. The combined solvent layers were evaporated at aspirator pressure, leaving 1.80 g. (79%) of white solid, m.p. 110-112°. Recrystallization from anhydrous ether yielded white needles of 6,13-diazadispiro[4.2.4.2]tetradecane (P-XII), m.p. 115-117°; infrared band at 3290  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{22}\text{N}_2$ : C, 74.17; H, 11.41; N, 14.43. Found: C, 74.08; H, 11.42; N, 14.08.

#### Preparation of 3,6-Di-*n*-butyl-2,5-piperazinedione.

As described for the preparation of P-III, a solution of 50.0 g. of 1-aminohexanoic acid in 200 ml. of  $\beta$ - $\beta$ '-dihydroxyethyl ether was refluxed in a 500 ml. round-bottomed flask for 4.5 hours. The solution was cooled to room temperature and the crystals which separated were filtered and washed with ethanol to yield 26.7 g. (62%) of crude product, m.p. 268-270°, reported (8) m.p. 269°; infrared bands at 3280, 3170, 3040 and 1660  $\text{cm}^{-1}$ .

#### Preparation of 2,5-Di-*n*-butylpiperazine.

The procedure is essentially that of Langenbeck, Augustin, Roehm and Hoffmann (9). A suspension of 25.0 g. of the above piperazinedione in 500 ml. of tetrahydrofuran was added to a stirred mixture of 17.0 g. of lithium aluminum hydride in 100 ml. of that solvent. The mixture was stirred and refluxed for 88 hours. After decomposition of the excess lithium aluminum hydride with 30% potassium hydroxide, the coagulated white precipitate was collected on a filter and extracted with hot tetrahydrofuran. The combined tetrahydrofuran solutions were evaporated at aspirator pressure and the residue was dissolved in anhydrous ether, then cooled in a refrigerator. The crystals which formed were collected on a filter, giving 10.9 g. (50%) of 2,5-di-*n*-butylpiperazine as white plates, m.p. 101-102° after two crystallizations from dry ether; infrared band at 3200  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{28}\text{N}_2$ : C, 72.66; H, 13.21; N, 14.12. Found: C, 72.95; H, 12.90; N, 14.10.

#### Low Pressure Hydrogenation of 12-Hydroxy-12-azadispiro[4.1.4.2]tridec-8-ene-6,13-dione (P-IV).

A suspension of 5.0 g. of P-IV, and 0.5 g. of Raney nickel in 50 ml. of absolute ethanol was shaken with hydrogen at 32 psi for 30 hours at room temperature. The mixture was then heated to dissolve the product and filtered through Filter Cell. The catalyst was washed with additional hot alcohol, the filtrates and washings were combined

and the ethanol removed at aspirator pressure, leaving 4.48 g. (96%) of white solid, m.p. 189-191°. Recrystallization from benzene-petroleum ether (b.p. 60-80°) yielded P-VII as white needles, m.p. 192-193°; infrared bands at 3200, 3100, 1760 and 1690  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{17}\text{NO}_2$ : C, 69.54; H, 8.27; N, 6.76. Found: C, 69.52; H, 8.30; N, 6.57.

#### High Pressure Hydrogenation of 12-Hydroxy-12-azadispiro[4.1.4.2]tridec-8-ene-6,13-dione (P-IV).

A solution of 10.0 g. of P-IV in 200 ml. of absolute ethanol was hydrogenated over 1.5 g. of Raney nickel at an initial pressure of 1900 psi and a final pressure of 1725 psi at 180° for 10 hours. The catalyst was removed by filtration and the filtrate evaporated at aspirator pressure, leaving 8.65 g. (91%) of white solid, m.p. 129-131°. Recrystallization from benzene-petroleum ether yielded P-VIII as white needles, m.p. 135-136°; infrared bands at 3380, 3150, 3050, and 1675  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{19}\text{NO}_2$ : C, 68.86; H, 9.15; N, 6.69. Found: C, 69.01; H, 9.13; N, 7.01.

#### Lithium Aluminum Hydride Reduction of 12-Azadispiro[4.1.4.2]tridecane-6,13-dione (P-VII).

A solution of 13.3 g. of P-VII in anhydrous tetrahydrofuran was added dropwise to a stirred suspension of 12 g. of lithium aluminum hydride in 300 ml. of that solvent. The mixture was refluxed 24 hours, then the excess hydride was destroyed with 30% potassium hydroxide solution. The mixture was filtered and the coagulated white precipitate was extracted with hot tetrahydrofuran. The combined solvent extracts were evaporated at aspirator pressure, leaving 12.1 g. (97%) of white solid, m.p. 123-125°. Recrystallization from benzene-petroleum ether yielded P-X as a white, granular solid, m.p. 126-128°; infrared bands at 3250, 3040 and 2680  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{21}\text{NO}$ : C, 73.79; H, 10.84; N, 7.17. Found: C, 73.80; H, 10.75; N, 7.08.

#### Oxidation of 6-Hydroxy-12-azadispiro[4.1.4.2]tridecane (P-X).

To a stirred solution of 3 g. of P-X in 30 ml. of water and 20 ml. of concentrated sulfuric acid was added slowly with stirring 20 ml. of 10% aqueous sodium dichromate. The solution was poured onto ice and 10% sodium hydroxide added until the solution was basic to litmus. The mixture was extracted with ether and the ether extract was washed and dried. Evaporation of the solvent gave an oily residue which was dissolved in petroleum ether. The solution was cooled and the flask scratched to yield 0.37 g. (12%) of unchanged P-X. The petroleum ether filtrate was evaporated and the oily residue was dried at 50° (2 mm.). After cooling to room temperature, the oil solidified to yield 2.28 g. (77%) of crude product, m.p. 40-44°. Sublimation of this material *in vacuo* gave white crystals of P-XI, m.p. 42-44°; infrared bands at 3320 and 1730  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{13}\text{NO}$ : C, 74.57; H, 9.91; N, 7.25. Found: C, 74.36; H, 9.60; N, 7.18.

#### Addition of Hydrogen Cyanide to 12-Hydroxy-12-azadispiro[4.1.4.2]tridec-8-ene-6,13-dione (P-IV).

To a stirred solution of 10 g. of P-IV in 60 ml. of ethanol and 2.46 g. of sodium cyanide in 30 ml. of water at 10-15° was added 4.90 g. of sulfuric acid in 20 ml. of ethanol and 40 ml. of water. The addition was over a 2 hour period and the temperature was maintained at 10-15°. The solution was stirred for an additional hour, then poured into water and the mixture extracted with chloroform. After drying the chloroform extract over anhydrous sodium sulfate, the solvent was removed at aspirator pressure to give an oil which was dissolved in benzene-petroleum ether and let stand overnight at room temperature. The crystals (4.59 g., 41%), m.p. 142-145° dec., which separated were crystallized from benzene-petroleum ether to yield the cyanohydrin, P-XI, m.p. 137-138° dec., which gave a red-purple color with ferric chloride; infrared bands at 3400, 3060, 2700, 2250, 1680 and 1620  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{19}\text{N}_2\text{O}_3$ : C, 62.89; H, 6.50; N, 11.29. Found: C, 63.27; H, 6.47; N, 10.85.

#### 12-Azadispiro[4.1.4.2]tridec-8-ene-6,13-dione (P-XVI).

A solution of 15 g. of P-IV in 400 ml. of ethanol and 15 g. of zinc dust was refluxed with stirring for 3 hours. The mixture was allowed to stand overnight at room temperature, then filtered and the residue washed with hot ethanol. The combined filtrates were evaporated nearly to dryness and 200 ml. of water was added to the residue. The mixture was extracted with chloroform and the chloroform extracts were washed with 10% sodium hydroxide and with water, then dried and the solvent removed by evaporation. The residue was

crystallized from benzene to yield 10.1 g. (72%) of P-XVI, m.p. 191-192°; infrared bands at 3130, 3040, 1760, 1680 and 1610  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{16}\text{NO}_2$ : C, 70.22; H, 7.36; N, 6.82. Found: C, 70.37; H, 7.62; N, 6.68.

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