98. Heterocyclic Spiro-naphthalenones. Part IV. Synthesis of Some 3,4-Dihydrospiro[naphthalene-2(1*H*),2′-pyrrolidine]-1-ols from 3,4-Dihydrospiro[furan-2(5*H*),1′(2′*H*)-naphthalene]-2′,5-dione[1])

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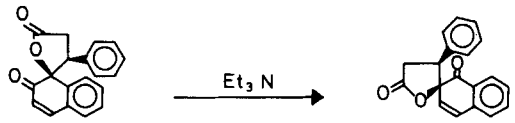
Summary

Depending on the experimental conditions the spirolactone **3** on treatment with methylamine gave compounds **6**, **7** or the rearranged product **4**. Compound **4** was used to prepare the title compounds **11**–**13**, **15**, **18**–**20** and other derivatives.

Introduction. – We have reported [2] the rearrangement of the spiro[naphthalene-tetrahydrofuran]dione **1** in methanolic triethylamine to the spirolactone **2**. We now present the rearrangement of the spirolactone **3** in the presence of methylamine to give the naphthalenone **4**. This rearrangement occurred after opening of the lactone ring by the amine. In this case triethylamine failed to promote any rearrangement.



1 **2**

Results. – *Reaction of the spirolactone* **3** *with methylamine.* The benzochromanone **5** [3] was opened with aqueous NaOH and cyclized with NBS to give the spiro[naphthalene-1,2′-tetrahydrofuran]dione **3** in good yield. The spirolactone **3** was opened with methylamine in methanol to yield the hydroxyamide **6**, whereas a large excess of methylamine in boiling methanol gave the rearranged product **4**. When excess methylamine was used in benzene, the spirolactone **3** was slowly transformed into the unstable imine **7** mixed with **4**. On prolonged standing this imine was converted into **4**.

Structure of compound **4**. The NMR. signal of H–C(2) in compound **8**, obtained by $NaBH_4$ reduction of **6**, is coupled with H–C(3) and H–C(4) which

[1]) A part of this work was presented at the 7th International Congress of Heterocyclic Chemistry at Tampa (Fla.) USA, August 12–17, 1979. Part III: [1].

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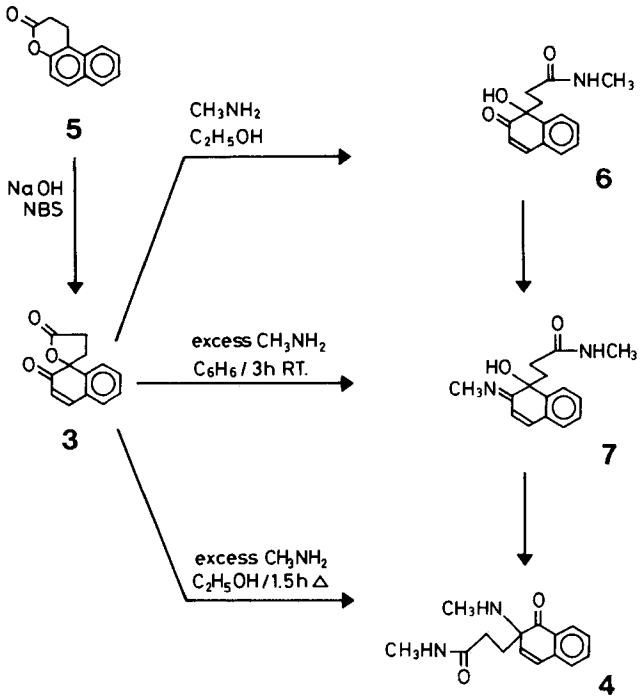
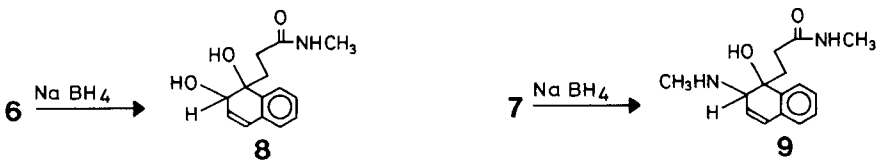
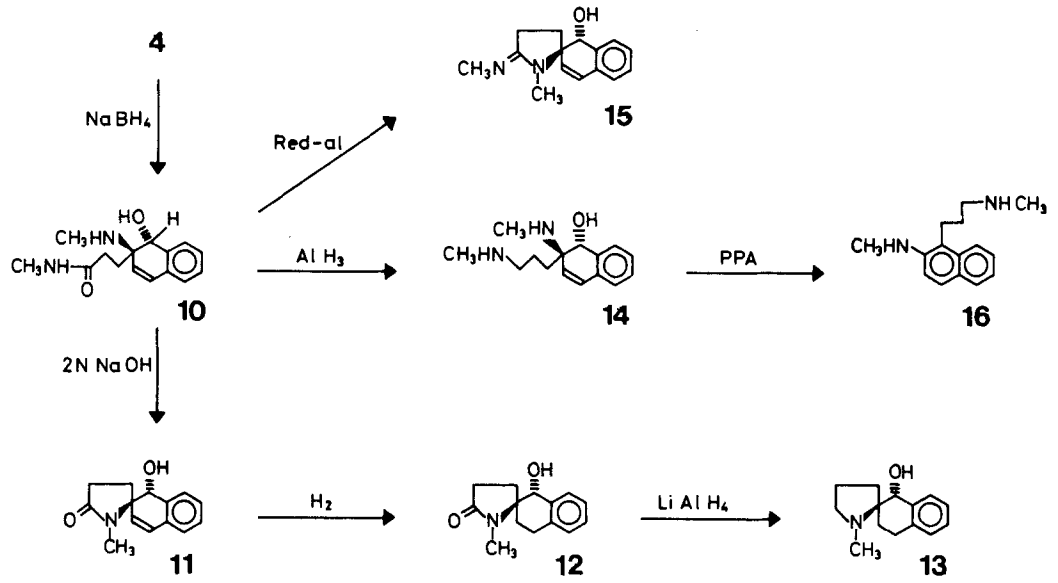


appear as multiplets; a similar coupling is also seen in the spectrum of the reduction product **9** of **7**. On the other hand, H–C(1) in the spectrum of the reduction product **10**, of **4**, appears as a singlet and both olefinic H–C(3) and H–C(4) as doublets, which supports the occurrence of a rearrangement comparable to that of **1** to **2** [2]. Final proof of the structure and configuration of compounds **4** and **10** was obtained when **10** was cyclized with 2N NaOH to the lactam **11**, hydrogenated to **12**, and subsequently reduced to give the spiro[naphthalene-2,2′-pyrrolidine]-2-ol **13** which has an NMR. spectrum identical with that of a product obtained by *Stoll* [5] by reducing and methylating the 1′-hydroxyspiro[pyrrolidine-2,2′-tetralin]-5-one [4][2]).

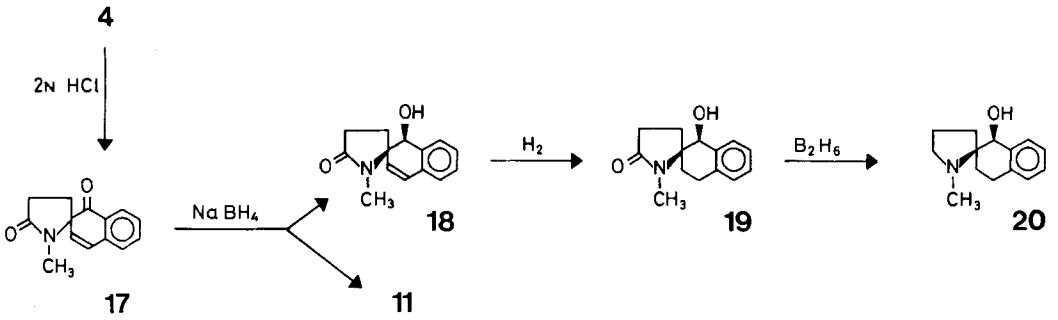


Reactions of **4** *and* **10**. Attempts to reduce the amide **10** to **14** with $LiAlH_4$ or *Red-al*[3]) gave the cyclic spiroamidine **15**. Compound **14** was finally obtained by reduction of **10** with AlH_3, formed *in situ* by the addition of $CHCl_3$ to a suspension of $LiAlH_4$ in THF[4]). Dehydrative rearrangement of **14** in polyphosphoric acid

[2]) Here we have used *A. P. Stoll* nomenclature.
[3]) A 70% solution of sodium bis(2-methoxyethoxy)-aluminium hydride in benzene.
[4]) This method may proceed following the equation: $CHCl_3 + 3\ LiAlH_4 \rightarrow 3\ AlH_3 + 3\ LiCl + CH_4$.



(PPA) gave the *N*-Methyl-2-(methylamino)-1-naphthalenepropanamine[5])[6]) (**16**). Compound **4** was readily cyclized with 2N HCl to the spiro[naphthalene-pyrrolidine]-dione **17** which was reduced by $NaBH_4$ to give the alcohols **18** and **11** (3:2). Compound **18** was hydrogenated to **19** which was reduced with B_2H_6 to the spiro-[naphthalene-pyrrolidine]-ol **20**.



Experimental Part

For general remarks on NMR. spectra see Part I [6].

3,4-Dihydrospiro[furan-2(5H),1'(2'H)-naphthalene]-2',5-dione[5])[7]) (**3**). The lactone **5** [3] (40 g, 0.202 mol) was dissolved under reflux in methanol (240 ml), H_2O (160 ml) and 2N NaOH (100 ml). The solution was cooled to −20° and NBS (35.6 g, 0.2 mol) in methanol (240 ml) and H_2O (60 ml)

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[5]) Throughout this paper chem. Abstracts nomenclature is given in the text; in the footnotes the IUPAC-Nomenclature is mentioned.

[6]) *N*-Methyl-3-(2'-methylamino-1'-naphthyl)propylamine.

[7]) Spiro[naphthalene-1(2*H*),2'-tetrahydrofuran]-2,5'-dione.

was slowly added. The reaction mixture was then allowed to reach 0° and was filtered. After drying, the compound was recrystallized from $CHCl_3$/petroleum ether to give 39.6 g (91%) of **3**; m.p. 138–139°. **Caution:** this compound is an eye and throat irritant. – ^{1}H-NMR.: 6.2 (*d*, J = 10, H–C(3')).

$C_{13}H_{10}O_3$ (214.2) Calc. C 72.9 H 4.7% Found C 72.6 H 4.7%

*1,2-Dihydro-1-hydroxy-*N*-methyl-2-oxo-1-naphthalenepropanamide*[5][8]) (**6**). Compound **3** (10 g, 47 mmol) was suspended in methanol (75 ml), then 33% CH_3NH_2 in ethanol (7.9 g, 84 mmol) was added with stirring and after 75 min at RT. the solution was evaporated to dryness. The residue was crystallized from methanol/petroleum ether to give 5.4 g (47%) of **6**; m.p. 159–161°. – ^{1}H-NMR.: 6.15 (*d*, J = 10, H–C(3)); 2.7 (*d*, CH_3N, collapsed to *s* after D_2O exchange).

$C_{14}H_{15}NO_3$ (245.3) Calc. C 68.6 H 6.2 N 5.7% Found C 68.2 H 6.1 N 5.4%

*1,2-Dihydro-1-hydroxy-*N*-methyl-2-(methylimino)-1-naphthalenepropanamide*[9]) (**7**) *mixed with* **4**. Compound **3** (5 g, 23 mmol) was suspended at RT. in benzene (50 ml) and anhydrous CH_3NH_2 (50 ml, 1.1 mol) at −20° was slowly added. After 3 h at RT. the clear solution was evaporated to dryness. A solution of 1,5-naphthalenedisulfonic acid (NDS) (4 g, 17.3 mmol) in ethanol (10 ml) added and the salt was allowed to crystallize overnight to give 7.3 g (78%) of a 2:1 mixture of **7** and **4** NDS salts which was not separated; m.p. 188–202°. – ^{1}H-NMR. of **7**: 6.9 (*d*, J = 10, H–C(4)); 6.4 (*d*, J = 10, H–C(3)); 3.3 (*s*, CH_3N=C(2)); 2.7 (*d*, CH_3NCO).

*1,2-Dihydro-*N*-methyl-2-(methylamino)-1-oxo-2-naphthalenepropanamide*[10]) (**4**) *1,5-naphthalenedisulfonate. From* **3**: compound **3** (80 g, 0.37 mmol) was suspended in methanol (800 ml), 33% CH_3NH_2 in ethanol (500 g, 5.3 mol) was added, and the mixture was heated under reflux for 1.5 h and kept overnight at RT. This solution was evaporated and the amine **4** was isolated as NDS salt (133 g, 88.5%), m.p. 250–253° (dec.) (C_2H_5OH/H_2O). – ^{1}H-NMR.: 8.0 (*d*×*d*, J = 3 and 10, H–C(8)); 6.7 (*d*, J = 10, H–C(4)); 6.0 (*d*, J = 10, H–C(3)); 2.55 (*d*, collapsed to *s* after D_2O exchange, CH_3NCO); 2.0 (*s*, CH_3N).

$C_{20}H_{22}N_2O_5S$ (402.5) Calc. C 59.7 H 5.5 N 7.0% Found C 59.2 H 5.6 N 6.7%

From **7**: a mixture of **7** and **4** was converted quantitatively to **4** when heated under reflux in methanol for 1 h.

*1,2-Dihydro-1,2-dihydroxy-*N*-methyl-1-naphthalenepropanamide*[11]) (**8**). Compound **6** (100 mg, 0.41 mmol) was dissolved in CH_3OH and treated with $NaBH_4$ (100 mg, 2.6 mmol) at 0–5° to give 30 mg (30%) of **8**; m.p. 137–138° ($CHCl_3$/ether). – ^{1}H-NMR.: 6.4 (*d*×*d*, J = 3 and 10, H–C(4)); 5.9 (*d*×*d*, J = 2 and 10, H–C(3)); 4.6 (narrow *m*, H–C(2)); 2.55 (*d*, collapsed to *s* after D_2O exchange, CH_3N).

$C_{14}H_{17}NO_3$ (247.3) Calc. C 68.0 H 6.9 N 5.7% Found C 67.8 H 7.0 N 5.6%

*1,2-Dihydro-1-hydroxy-*N*-methyl-2-(methylamino)-1-naphthalenepropanamide*[12]) (**9**). A 2:1 mixture of bases **7** and **4** prepared from the mixture of NDS salts (20.1 g, 50 mmol) was dissolved in methanol (200 ml) and reduced at 0–5° with $NaBH_4$ (1 g, 26 mmol) added in small portions. After the usual work-up, the oily residue was crystallized from $CHCl_3$/ether to give 4.5 g (35%) of **9**; m.p. 122–123°. – ^{1}H-NMR.: 6.3 (*d*×*d*, J = 3 and 10, H–C(4)); 5.9 (*d*×*d*, J = 2 and 10, H–C(3)); 3.5 (narrow *m*, H–C(2)).

$C_{15}H_{20}N_2O_2$ (260.3) Calc. C 69.2 H 7.7 N 10.8% Found C 69.0 H 8.0 N 10.6%

*(1*RS,2RS*)-1,2-Dihydro-1-hydroxy-*N*-methyl-2-(methylamino)-2-naphthalenepropanamide*[13]) (**10**) *1,5-naphthalenedisulfonate.* Compound **4** was reduced at 0–5° with $NaBH_4$ by the usual procedure to

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[8]) *N*-Methyl-3-(1-hydroxy-2-oxo-1,2-dihydro-1-naphthyl)-propionamide.

[9]) *N*-Methyl-3-(1-hydroxy-2-methylimino-1,2-dihydro-1-naphthyl)-propionamide.

[10]) *N*-Methyl-3-(2-methylamino-1-oxo-1,2-dihydro-2-naphthyl)-propionamide.

[11]) *N*-Methyl-3-(1,2-dihydroxy-1,2-dihydro-1-naphthyl)-propionamide.

[12]) *N*-Methyl-3-(1-hydroxy-2-methylamino-1,2-dihydro-1-naphthyl)-propionamide.

[13]) (1*RS*,2*RS*)-*N*-Methyl-3-(1-hydroxy-2-methylamino-1,2-dihydro-2-naphthyl)-propionamide.

give **10** in 62% yield; m.p. 115–116°, NDS salt 205–206° dec. – ^{1}H-NMR.: 6.45 (*d*, *J* = 10, H–C(4)); 5.7 (*d*, *J* = 10, H–C(3)); 5.0 (*s*, H–C(1)).

$C_{20}H_{24}N_2O_5S$ (404.5) Calc. C 59.4 H 6.0 N 6.9% Found C 59.6 H 6.0 N 6.9%

trans-*1-Hydroxy-1'-methyl-spiro[naphthalene-2(1H),2'-pyrrolidine]-5'-one* (**11**). Compound **10** (23 g, 88 mmol) was dissolved in methanol (115 ml), 2N NaOH (1150 ml) was added and the mixture was heated under reflux for 3 h. The solution was cooled to −20° and filtered, the solid was recrystallized from ethyl acetate to give 11.5 g (57%) of **11**; m.p. 206–207°. – ^{1}H-NMR.: 6.4 (*d*, *J* = 10, H–C(4)); 5.75 (*d*, *J* = 10, H–C(3)); 5.2 (*d*, collapsed to *s* after D_2O exchange, H–C(1)).

$C_{14}H_{15}NO_2$ (229.3) Calc. C 73.3 H 6.6 N 6.1% Found C 73.1 H 6.4 N 5.9%

trans-*3,4-Dihydro-1-hydroxy-1'-methyl-spiro[naphthalene-2(1H),2'-pyrrolidine]-5'-one*[14]) (**12**). Compound **11** in methanol and Pd/C 5.4% was hydrogenated under normal conditions to give **12** in quantitative yield; m.p. 203–205° (methanol/H_2O). – ^{1}H-NMR.: 4.95 (*d*, collapsed to *s* after D_2O exchange, H–C(1)); 2.9 (*s*, CH_3N).

$C_{14}H_{17}NO_2$ (231.3) Calc. C 72.7 H 7.4 N 6.1% Found C 72.9 H 7.3 N 6.0%

trans-*1,2,3,4-Tetrahydro-1'-methyl-spiro[naphthalene-2,2'-pyrrolidine]-1-ol* (**13**)[15]) *1,5-naphthalenedisulfonate.* Compound **12** (231 mg, 1 mmol) was reduced with $LiAlH_4$ (95 mg, 2.5 mmol) in THF (10 ml) at RT. for 25 min followed by usual work-up. Compound **13** was isolated as NDS salt (25 mg, 7%); m.p. 232–237°. – ^{1}H-NMR.: 7.15 (*m*, 4 arom. H); 4.65 (*s*, H–C(1)); 4.5 (br. *s*, HO); (*s*, H_3CN).

$C_{19}H_{23}NO_4S$ (361.5) Calc. C 63.1 H 6.4 N 3.9% Found C 62.8 H 6.3 N 4.0%

trans-*1,2,3,4-Tetrahydro-1'-methyl-5'-methylimino-spiro[naphthalene-2,2'-pyrrolidine]-1-ol*[16]) (**15**). Compound **10** (13 g of base, 0.05 mol) dissolved in THF (200 ml) was added dropwise to a solution of *Red-al*®) (64 g, ~0.2 mol) in THF (400 ml). The solution was kept 1.5 h at RT. and worked up to give 5.5 g (45%) of **15**; m.p. 276–280° (methanol). – ^{1}H-NMR.: 6.5 (*d*, *J* = 10, H–C(4)); 5.8 (*d*, *J* = 10, H–C(3)); 2.9 and 2.8 (2 *s*, 2 CH_3N).

$C_{15}H_{18}N_2O$ (242.3) Calc. C 74.3 H 7.5 N 11.6% Found C 74.1 H 7.8 N 11.1%

(1RS,2RS)-1,2-Dihydro-2-(methylamino)-2-[3-(methylamino)propyl]-1-naphthalenol[17]) (**14**) *dihydrochloride.* Compound **10** (19.5 g of base, 0.075 mol) dissolved in THF (250 ml) and $CHCl_3$ (6 g, 0.05 mol) was added dropwise to a suspension of $LiAlH_4$ (8.55 g, 0.225 mol) in THF (300 ml). The mixture was heated under reflux for 1 h. After the usual work-up, **14** was isolated as dihydrochloride (18.6 g, 78%); m.p. 205–207° (ethanol/ether). – ^{1}H-NMR.: 6.4 (*d*, *J* = 10, H–C(4)); 5.8 (*d*, *J* = 10, H–C(3)); 5.0 (*s*, H–C(1)); 2.35 and 2.15 (2 *s*, 2 CH_3N).

$C_{15}H_{24}Cl_2N_2O$ (319.3) Calc. C 56.4 H 7.6 N 8.8% Found C 56.1 H 7.6 N 8.6%

N-*Methyl-2-(methylamino)-1-naphthalenepropanamine*[18]) (**16**) *1,5-naphthalenedisulfonate.* Compound **14** dihydrochloride (8.4 g) was mixed with PPA (130 g) and heated to 90–100° for 30 min. The solution was poured into H_2O, made alkaline and extracted. Compound **16** was isolated as NDS salt (12.2 g, 90%); m.p. 218–224° (methanol/H_2O). – ^{1}H-NMR.: 8.0–7.0 (*m*, 6 H ar.); 2.9 (*s*, CH_3N–C(2)); 2.4 (*s*, CH_3N-alkyl).

$C_{25}H_{28}N_2O_6S_2$ (516.6) Calc. C 58.1 H 5.5 N 5.4% Found C 58.3 H 5.6 N 5.7%

1'-Methyl-spiro[naphthalene-2(1H),2'-pyrrolidine]-1,5'-dione (**17**). Compound **4** (10 g, 38.7 mmol) was heated 3 h under reflux in 2N HCl (250 ml). This solution was cooled and made alkaline in

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[14]) *trans*-1-Hydroxy-1'-methyl-spiro[1,2,3,4-tetrahydro-naphthalene-2,2'-pyrrolidine]-5'-one.

[15]) *trans*-1'-Methyl-spiro[1,2,3,4-tetrahydronaphthalene-2,2'-pyrrolidine]-1-ol.

[16]) *trans*-1'-Methyl-5'-methylimino-spiro[1,2,3,4-tetrahydronaphthalene-2,2'-pyrrolidine]-1-ol.

[17]) (1*RS*,2*RS*)-2-Methylamino-2-[(3-methylamino)propyl]-1,2-dihydronaphthalene-1-ol.

[18]) *N*-Methyl-3-(2-methylamino-1-naphthyl)-propylamine.

order to liberate **17** which behaved as a base; 7.5 (85%) of **17** were obtained; m.p. 91–94°. – ^{1}H-NMR.: 6.85 (*d*, $J = 10$, H–C(4)); 6.2 (*d*, $J = 10$, H–C(3)); 2.65 (*s*, CH_3N).

$C_{14}H_{13}NO_2$ (227.3) Calc. C 74.0 H 5.8 N 6.2% Found C 73.8 H 5.8 N 6.3%

cis- *and* trans-*1-Hydroxy-1'-methyl-spiro[naphthalene-2(1H),2'-pyrrolidine]-5'-one*[19]) (**18** *and* **11**). Compound **17** (20 g, 0.088 mol) was reduced at 0–5° with $NaBH_4$ (3.52 g, 0.088 mol) in methanol (200 ml). A 2:3 mixture of the isomers **11** and **18** was isolated (16.8 g, 83%). This mixture was dissolved in 2-propanol (100 ml) and pure **18** crystallized (4.5 g, 22%); m.p. 170–175°. – ^{1}H-NMR.: 6.75 (*d*, $J = 10$, H–C(4)); 5.7 (*d*, $J = 10$, H–C(3)); 4.8 (*d*, collapsed to *s* after D_2O exchange, H–C(1)); 2.4 (*s*, CH_3N).

$C_{14}H_{15}NO_2$ (229.3) Calc. C 73.3 H 6.6 N 6.1% Found C 73.1 H 6.8 N 6.1%

A small amount of the mother liquor was chromatographed on silica gel TLC. plates (heptane/$CHCl_3$/ethanol; 65:35:10) to isolate a pure sample of **11** (highest Rf value); m.p. 206–207°. – ^{1}H-NMR.: superimposable with **11** obtained from **10**.

cis-*3,4-Dihydro-1-hydroxy-1'-methyl-spiro[naphthalene-2(1H),2'-pyrrolidine]-5'-one*[20]) (**19**). Compound **18** (130 g, 0.57 mol) in methanol (2.5 l) and Pd/C 5.4% (5 g) was hydrogenated under normal conditions to give **19** (125.5 g, 96%); m.p. 183–185° ($CHCl_3$/ether). – ^{1}H-NMR.: 4.5 (*d*, collapsed to *s* after D_2O exchange, H–C(1)); 2.9 (*s*, CH_3N).

$C_{14}N_{17}NO_2$ (231.3) Calc. C 72.7 H 7.4 N 6.1% Found C 72.3 H 7.3 N 6.0%

cis-*3,4-Dihydro-1'-methyl-spiro[naphthalene-2(1H),2'-pyrrolidine]-1-ol*[21]) (**20**). Compound **19** (1.15 g, 5 mmol) in THF (15 ml) was reduced with 1M B_2H_6/THF (*Aldrich*, 10 ml) under reflux for 3 h. After the usual work-up, 800 mg (74%) of **20** were isolated; m.p. 88–91° (petrol. ether). – ^{1}H-NMR.: 4.1 (*s*, H–C(1)); 2.4 (*s*, CH_3N).

$C_{14}H_{19}NO$ (217.3) Calc. C 77.4 H 8.8 N 6.5% Found C 77.0 H 8.8 N 6.5%

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[5] *A.P. Stoll*, private communication.
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[19]) *cis-* and *trans*-1-Hydroxy-1'-methyl-spiro[1,2-dihydronaphthalene-2,2'-pyrrolidine]-5'-one.
[20]) *cis*-1-Hydroxy-1'-methyl-spiro[1,2,3,4-tetrahydronaphthalene-2,2'-pyrrolidine]-5'-one.
[21]) *cis*-1'-Methyl-spiro[1,2,3,4-tetrahydronaphthalene-2,2'-pyrrolidine]-1-ol.