189. Heterocyclic Spiro-naphthalenones

Part VI. Some Reactions with Spiro[naphthalene-2(1*H*),2′-pyrrolidine]-1,5′-dione Leading to Various 6-, 7-, 8-, 9-, 10- and 11-membered Azacycloalkanes[1])[2])

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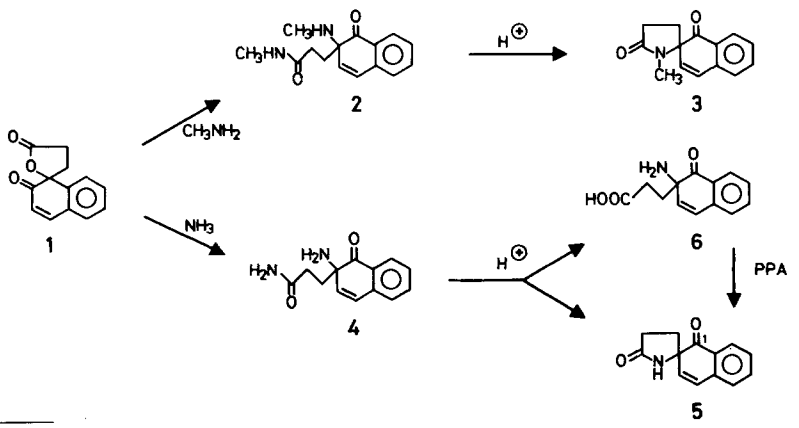
(1.VII.80)

Summary

The spirolactam **5** was reduced to the spiro[naphthalene, pyrrolidine] **7** which was *N*-aralkylated to give **9** and **17**. Cyclization of **9** gave the phenanthridines **10** and **11**; similarly, **17** afforded the 7- and 8-membered heterocycles **18** and **19**. Compounds **10**, **18** and **19** when subjected to an intramolecular *Hofmann* elimination yielded the 9-, 10- and 11-membered ring systems, respectively **16**, **22** and **23**.

In an earlier communication [2] we reported the transformation of the spirolactone **1** with methylamine to the naphthalenepropanamide **2**[3]), the cyclization of the latter to the *N*-methylspirolactam **3**, and the reduction of **3** to various *N*-methyl-spiro[naphthalene-2,2′-pyrrolidine]-1-ols. In this paper, we study some

Scheme 1



[1]) This work was presented at the 7th International Congress of Heterocyclic Chemistry at Tampa (Fla.) USA, August 12–17, 1979.

[2]) Part V: [1].

[3]) For the nomenclature, see [2] footnote 5.

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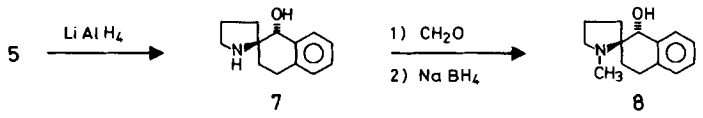
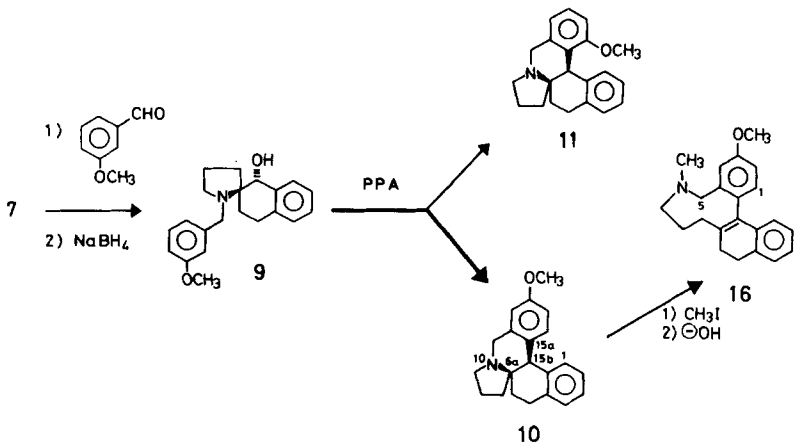
synthetic routes of more complex heterocycles, starting from the *N*-aralkylated spiro[naphthalene-2,2′-pyrrolidine]-1-ols **9** and **17**, these being prepared form the *N*-unsubstituted spirolactam **5**. Treatment of **1** with ammonia gave **4** which, in the presence of HCl, furnished the desired lactam **5** and the amino acid **6** (4:3). The latter was converted into **5** on heating in polyphosphoric acid (PPA) *(Scheme 1)*. $LiAlH_4$ reduction of **5** led to **7**. For proof of structure, **7** was *N*-methylated with formaldehyde in the presence of $NaBH_4$, giving the known compound **8** [2] *(Scheme 2)*. The alcohol **7** was treated with 3-methoxybenzaldehyde and $NaBH_4$ to yield **9**.

Scheme 2



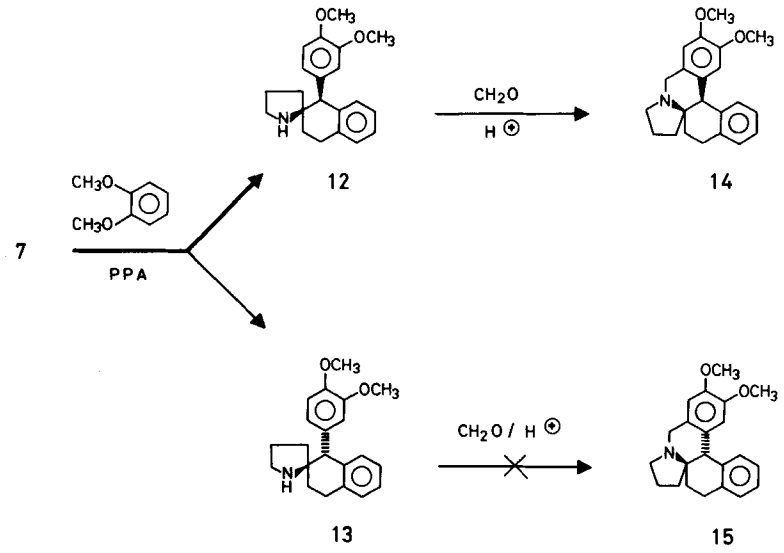
Compound **9** was cyclized with PPA at RT. to the phenanthridines **10** and **11** (3:1) *(Scheme 3)*. Models show that the structure having C(15b), C(15a)- and C(6a),N-bonds in *cis* positions is less rigid and less strained than the *trans* structure. Furthermore, such a cyclization which readily takes place at RT. should proceed *via* an S_N2 type of mechanism and therefore should give mainly the *cis* isomer; in this case the PPA-activated hydroxy leaving group would be attacked by the strongly nucleophilic methoxyphenyl group. Consequently, it is assumed that the main product **10** has a *cis* configuration as shown in *Scheme 3*. The by-product **11** was shown by X-ray structure analysis [3] to have a *cis* configuration, as had been postulated for **10**. It differed from **10** only by the position of the methoxy group.

Scheme 3

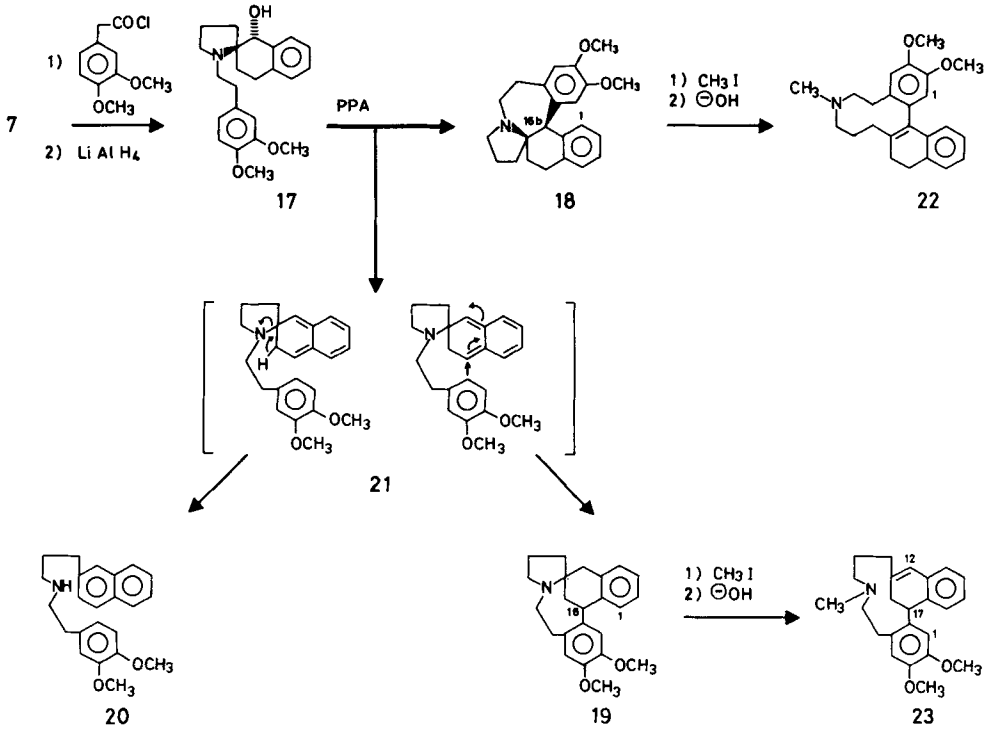


In an attempt to obtain a compound with a *trans* configuration (**15**), compound **7** was allowed to react with veratrole in PPA, giving a mixture of **12** and **13** (4:1) *(Scheme 4)* which was separated. Again the main product **12** was assumed to be the *cis* isomer, formed *via* the S_N2 type of mechanism. As the ^{1}H-NMR. spectra of

Scheme 4



Scheme 5



12 and **13** were almost superimposable it was concluded that the minor product **13** must be the *trans* isomer. Both isomers were treated with formaldehyde in HCl, but only **12** reacted to give **14**. Under these conditions the strained *trans* structure **15** could not be formed from **13** which was recovered unchanged, giving a further proof of the stereochemistry assigned to this series.

Compound **10** reacted with methyl iodide and the quaternary salt was treated with aqueous NaOH to give, by intramolecular *Hofmann* elimination, the 9-membered heterocycle **16**.

In order to obtain the 7-membered homologue **18** of **14**, **7** was acylated with 3,4-dimethoxyphenylacetyl chloride and subsequently reduced with $LiAlH_4$ to give **17**. On treatment with PPA at RT., this compound gave mainly the desired product **18** and, as by-products, the 8-membered heterocycle **19** and the *N*-phenylethyl-2-naphthalenepropanamine **20** *(Scheme 5)*. Structure **21** is postulated as an intermediate in the formation of **19** and **20**. No clear conclusions about the configuration of compounds **18** and **19** could be drawn from the ^{1}H-NMR. spectra but, as for compounds **10** and **12**, a *cis* configuration was assigned to **18**.

When compounds **18** and **19** reacted with methyl iodide, they gave quaternary salts which were converted, again by intramolecular *Hofmann* elimination, into the 10- and 11-membered heterocycles **22** and **23**.

Experimental Part

For general remarks on ^{1}H-NMR. spectra see [4].

Spiro[naphthalene-2(1H),2'-pyrrolidine]-1,5'-dione (**5**) and *2-amino-1,2-dihydro-1-oxo-2-naphthalenepropanoic acid* (**6**) *hydrochloride*. To a suspension of the spirolactone **1** [2] (214.2 g, 1 mol) in ethanol (1000 ml) at RT., gaseous NH_3 (140 g, 8.2 mol) was added with stirring, kepping the temperature below 35°. The reaction mixture became clear and yellowish. The excess of NH_3 was allowed to evaporate overnight and the reaction mixture was evaporated to dryness under vacuum to give 230 g of the crude 2-naphthalenepropanamide **4**. This oil was very slowly added to a mixture of conc. hydrochloric acid (500 ml) and crushed ice (500 g) and kept at RT. for 15 h. Ice (500 g) was added, the solution was brought to pH 7.5 by addition of a 30% aqueous solution of NaOH, extracted with $CHCl_3$, dried and evaporated to dryness. The residue was recrystallized from $CHCl_3$ to give 85.5 g (40%) of **5**, m.p. 201–206°. – ^{1}H-NMR.: 6.8 (*s*, HN); 6.6 (*d*, $J=10$, H–C(4)); 6.1 (*d*, $J=10$, H–C(3)).

$C_{13}H_{11}NO_2$ (213.2) Calc. C 73.2 H 5.2 N 6.6% Found C 73.1 H 5.4 N 6.5%

The aqueous layer was filtered to collect the light brown powder which had precipitated during the extraction process. This product was washed twice with H_2O and dried under vacuum at 60° to give 70 g (30%) of crude **6**, m.p. 188–200°. Part was converted to the hydrochloride and recrystallized from ethanol/ether, m.p. 186–189°. – ^{1}H-NMR. (HCl salt in CD_3OD): 7.05 (*d*, $J=10$, H–C(4)); 6.3 (*d*, $J=10$, H–C(3)); 2.3 (*s*, CH_2CH_2).

$C_{13}H_{14}ClNO_3$ (267.7) Calc. C 58.3 H 5.3 N 5.2% Found C 58.3 H 5.3 N 5.3%

Compound **6** (100 mg, 0.43 mmol) was heated in PPA (5 g) at 100° for 5 min. The hot solution was poured onto ice, made alkaline with 30% NaOH (pH 8) and extracted with CH_2Cl_2. The organic layer was dried and evaporated to give 77 mg (84%) of crystalline **5**, identical with the compound obtained from **4**.

trans-*3,4-Dihydro-spiro[naphthalene-2(1H),2'-pyrrolidine]-1-ol* (**7**). A solution of the spirolactam **5** (42.6 g, 0.2 mol) in THF (1200 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (38 g,

1.0 mol) in THF (800 ml). The mixture was heated under reflux for 75 min, then cooled to about 0° and 2N NaOH (100 ml) was cautiously added. The reaction mixture was filtered through Kieselguhr, dried and evaporated to dryness. The crude product was recrystallized from toluene to give 38.5 g (95%) of pure **7**, m.p. 123–127°. – ^{1}H-NMR.: 4.45 (*s*, H–C(1)); 3.0 (br. *s*, HN and HO).

$C_{13}H_{17}NO$ (203.3) Calc. C 76.8 H 8.4 N 6.9% Found C 76.6 H 8.8 N 6.9%

trans-*3,4-Dihydro-1'-methyl-spiro[naphthalene-2(1*H*),2'-pyrrolidine]-1-ol* (**8**). To compound **7** (203 mg, 1 mmol) in methanol (10 ml), was added an aqueous ~35% solution of formaldehyde (0.5 g, ~5 mmol), the mixture was heated at 60° for 15 min and then cooled to 0–5°. $NaBH_4$ (100 mg, 2.65 mmol) was added in 2 portions. After 1 h the reaction was worked up to give 180 mg of **8** as an oil (^{1}H-NMR. identical with that of an authentic sample of **8** [2]).

trans-*3,4-Dihydro-1'-[(3-methoxyphenyl)methyl]-spiro[naphthalene-2(1*H*),2'-pyrrolidine]-1-ol* (**9**) *hydrochloride*. To compound **7** (10.15 g, 0.05 mol) in methanol (500 ml), was added 3-methoxybenzaldehyde (34 g, 0.25 mol), and the reaction mixture was heated under reflux for 1 h, then cooled to 0–5°. $NaBH_4$ (3.5 g, 0.093 mol) was added in 7 portions and the mixture was stirred for 1 h. After working up the residue was treated with HCl/ether and the solid recrystallized from ethanol/ether to give 11 g (61%) of **9** hydrochloride; m.p. 213–216°.

$C_{21}H_{26}ClNO_2$ (359.9) Calc. C 70.1 H 7.3 N 3.9% Found C 69.4 H 7.5 N 3.8%

cis-*5,6,8,9,11,15b-Hexahydro-13-methoxy-7*H*-benzo[a]pyrrolo[2,1-e]phenanthridine* (**10**) and *15-methoxy analogue* (**11**) *hydrochloride*. Compound **9** hydrochloride (44 g, 0.122 mol) was stirred in PPA (1200 g) at RT. for 1.5 h. The mixture was poured into H_2O, ice was added, and the solution was made alkaline with 30% NaOH. The $CHCl_3$ extract was dried and evaporated to dryness. The residue was treated with ether and cooled to 5° overnight. The solid was recrystallized from hexane, giving 20.8 g (56%) of pure **10**, m.p. 124–126°. – ^{1}H-NMR.: 7.15 (*s*, H–C(1), H–C(2), H–C(3) and H–C(4)); 6.9–6.5 (*m*, H–C(12), H–C(14) and H–C(15)); 3.8 (narrow *m*, $H_2C(11)$ and H–C(15b)); 3.75 (*s*, CH_3O); 2.8 (*m*, $H_2C(5)$ and $H_2C(9)$); 1.7 (*m*, $H_2C(6)$, $H_2C(7)$ and $H_2C(8)$).

$C_{21}H_{23}NO$ (305.4) Calc. C 82.6 H 7.6 N 4.6% Found C 82.5 H 7.5 N 4.8%

The mother liquor was evaporated to dryness, dissolved in ethanol, cooled to 5° for 2 h and filtered to give 4.9 g (13%) of the isomer **11**, m.p. 129–131°, HCl salt 252–253°. – ^{1}H-NMR.: 7.4–6.6 (*m*, 7 H arom.); 4.55 (*s*, H–C(15b)); 3.9 (*s*, CH_3O); 3.4 (*s*, $H_2C(11)$).

$C_{21}H_{24}ClNO$ (341.9) Calc. C 73.8 H 7.1 N 4.1% Found C 73.4 H 7.1 N 4.1%

*6,7,8,9,10,11-Hexahydro-3-methoxy-6-methyl-5*H*-benzo[c]naphth[1,2-e]azonine* (**16**) *hydrochloride*. To compound **10** (7.8 g, 0.0255 mol) in acetone (100 ml) was added CH_3I (3.65 g, 0.0255 mol). After standing for 17 h at RT. the product was allowed to crystallize at 5°, yielding 11.1 g (97%) of the methylammonium iodide, m.p. 255–256°.

$C_{22}H_{26}INO$ (447.4) Calc. C 59.1 H 5.9 N 3.1% Found C 59.0 H 5.9 N 3.1%

To a solution of the above methylammonium iodide (10.8 g, 0.024 mol) in methanol (200 ml) was added 10% KOH in H_2O (400 ml). This mixture was heated under reflux for 1 h and extracted with CH_2Cl_2. After drying and evaporating the organic layer, the product was treated with HCl/ether and recrystallized from ethanol/ether, giving 4.35 g (51%) of **12** hydrochloride, m.p. 187–192°. – ^{1}H-NMR.: 7.3–6.4 (*m*, 7 H arom.); 3.85 (*s*, CH_3O); 3.75 and 3.45 (2 *d*, $J_{(AB)} = 14$, $H_2C(5)$); 2.4 (*s*, CH_3N).

$C_{22}H_{26}ClNO$ (355.9) Calc. 74.2 H 7.4 N 3.9% Found C 74.1 H 7.5 N 4.0%

cis-*3,4-Dihydro-1-(3,4-dimethoxyphenyl)-spiro[naphthalene-2(1*H*),2'-pyrrolidine]* (**12**) *hydrochloride* and the trans-*analogue* (**13**) *hydrochloride*. Compound **7** (50.7 g, 0.25 mol) and veratrole (69 g, 0.5 mol) were heated in PPA (1200 g) at 60° for 45 min. The mixture was poured into H_2O, ice was added, and the solution was made alkaline. The product was extracted with CH_2Cl_2, and the extract was dried and evaporated. The crude base was treated with HCl/ether and ethanol to give 60 g (67%) of **12** hydrochloride, m.p. 262–266°. – ^{1}H-NMR. (C_6D_6): 7.3–6.5 (*m*, 7 H arom.); 3.9 (*s*, H–C(1)); 3.45 (*s*, 2 CH_3O).

$C_{21}H_{26}ClNO_2$ (359.9) Calc. C 70.1 H 7.3 N 3.9% Found C 70.1 H 7.4 N 4.1%

The mother liquor was evaporated to dryness and dissolved in ethanol (150 ml). Ether (150 ml) was added and **13** hydrochloride crystallized overnight yielding 14.1 g (16%), m.p. 260–265°. – ^{1}H-NMR. (C_6D_6): 7.3–6.6 (*m*, 7 H arom.); 3.85 (*s*, H–C(1)); 3.45 (*s*, 2 CH_3O).

$C_{21}H_{26}ClNO_2$ (359.9) Calc. C 70.1 H 7.3 N 3.9% Found C 69.9 H 7.5 N 3.8%

cis-*5,6,8,9,10,15b-Hexahydro-13,14-dimethoxy-7*H-*benzo[a]pyrrolo [2,1-e]phenanthridine* (**14**). To compound **12** (11.6 g, 0.0322 mol) in 2N HCl (70 ml) was added aqueous formaldehyde (23 ml, 35%, 0.23 mol). The mixture was heated for 45 min at 100°, then cooled, made alkaline and extracted with CH_2Cl_2. The extract was evaporated and the residue was recrystallized from ether at −20° to give 6.3 g (58%) of **14**, m.p. 129–131°. – ^{1}H-NMR.: 7.1 (*s*, H–C(1), H–C(2), H–C(3) and H–C(4)); 6.65 and 6.5 (2 *s*, H–C(12) and H–C(15)); 3.8 and 3.7 (2 *s*, 2 CH_3O); 3.8 (narrow *m*, H_2C(11) and H–C(15b)).

$C_{22}H_{25}NO_2$ (335.5) Calc. C 78.8 H 7.5 N 4.2% Found C 78.7 H 7.7 N 4.0%

trans-*3,4-Dihydro-1'-[2-(3,4-dimethoxyphenyl)ethyl]-spiro[naphthalene-2(1*H*),2'-pyrrolidine]-1-ol*(**17**) *hydrochloride.* Homoveratric acid (88.5 g, 0.45 mol) was added to a solution of $SOCl_2$ (59.5 g, 0.5 mol) in CH_2Cl_2 (900 ml), the reaction mixture was heated under reflux for 1 h and its volume was then reduced to 500 ml.

To compound **7** (92 g, 0.45 mol) in CH_2Cl_2 (2000 ml), was added triethylamine (229 ml, 1.64 mol) and the mixture was cooled to 0–5°. The above solution of 3,4-dimethoxyphenylacetyl chloride (500 ml) was added dropwise with stirring during a period of 45 min. The mixture was kept for a further 30 min at 0–5°, then overnight at RT. The mixture was washed successively with H_2O (500 ml), 1N NaOH (500 ml), 2N HCl (1000 ml) and finally with H_2O (500 ml). After drying and evaporating to dryness, the residue was crystallized by the addition of ether. The product was dried under vacuum at 60° to give 104 g (61%) of crude trans-*3,4-dihydro-1'-(3,4-dimethoxyphenyl)acetyl-spiro[naphthalene-2(1*H*),2'-pyrrolidine]-1-ol,* m.p. 166–172°. This crude amide (104 g, 0.273 mol) was suspended in THF (1000 ml). $LiAlH_4$ (26 g, 0.682 mol) was added portionwise with stirring at RT. After the end of the addition the mixture was heated under reflux for 15 min and then cooled to 0–5°. 1N NaOH (100 ml) was added cautiously and the mixture was filtered through Kieselguhr, dried and evaporated. The product **17** was isolated as hydrochloride (89 g, 81%), m.p. 198–201° (ethanol/ether). – ^{1}H-NMR.: 7.7–6.6 (*m*, 7 arom.); 4.45 (*s*, H–C(1)); 3.85 (*s*, 2 CH_3O); 2.8 (br. signal, HO).

$C_{23}H_{30}ClNO_3$ (404.0) Calc. C 68.4 H 7.5 N 3.5% Found C 67.9 H 7.6 N 3.8%

cis-*5,8,9,11,12,16b-Hexahydro-14,15-dimethoxy-6*H,*7*H-*benzo[d]naphtho[2,1-b]pyrrolo[1,2-a]-azepine* (**18**), N-*[2-(3,4-dimethoxyphenyl)ethyl]-2-naphthalenepropanamine* (**20**) *hydrochloride* and *5,7,8,10,15b-hexahydro-13,14-dimethoxy-6* H, *5a,16-methanodibenzo [d,g]pyrrolo [1,2-a]azocine* (**19**). Compound **17** hydrochloride (83 g, 0.205 mol) was stirred in PPA (1000 g) at RT. for 17 h. This mixture was poured into H_2O, made alkaline with 30% NaOH (~2250 ml) and the $CHCl_3$ extract was dried and evaporated. The residue was recrystallized from ether to give 29 g (41%) of **18**, m.p. 136–138°. – ^{1}H-NMR.: 7.2–6.7 (*m*, H–C(1), H–C(2), H–C(3) and H–C(4)); 6.7 and 6.1 (2 *s*, H–C(13) and H–C(16)); 4.0 (*s*, H–C(16b)); 3.85 and 3.6 (2 *s*, 2 CH_3O).

$C_{23}H_{27}NO_2$ (349.5) Calc. C 79.0 H 7.8 N 4.0% Found C 78.9 H 7.8 N 4.2%

The etheral mother liquor was evaporated and the residue treated with 1,5-naphthalenedisulfonic acid (NDS) and ethanol to give 6.7 g (7%) of **20** NDS salt; m.p. 268–271°. The liberated base was converted to the hydrochloride which was recrystallized from ethanol, yielding 4.2 g (5%), m.p. 202–207°. – ^{1}H-NMR.: 7.9–7.0 (*m*, 7 H naphth., pattern corresponding to 2-alkylated naphthalene); 6.7 (*s*, 3 H arom.); 3.8 (*s*, 2 CH_3O); 1.25 (*s*, HN).

$C_{23}H_{28}ClNO_2$(386.0) Calc. C 71.6 H 7.3 N 3.6% Found C 71.6 H 7.2 N 3.8%

The ethanolic mother liquor was left for 3 weeks at RT., yielding 5.5 g of crude **19** NDS salt. The liberated base was recrystallized from ethanol, giving 2.6 g (3.6%), m.p. 150–153°. – ^{1}H-NMR.: 7.1 (narrow *m*, H–C(1), H–C(2), H–C(3) and H–C(4)); 6.85 and 6.4 (2 *s*, H–C(12) and H–C(15)); 4.2 (*d*×*d*, *J*=3 and 8, H–C(16)); 3.9 and 3.8 (2 *s*, 2 CH_3O).

$C_{23}H_{27}NO_2$ (349.5) Calc. C 79.0 H 7.8 N 4.0% Found C 78.5 H 7.7 N 4.1%

*5,6,7,8,9,10,11,12-Octahydro-2,3-dimethoxy-7-methyl-benzo[*d*]naphtho[1,2-*f*]azecine* (**22**). To compound **18** (10.5 g, 0.03 mol) in acetone (200 ml) was added methyl iodide (4.7 g, 0.33 mol). After 16 h at RT., then 30 min at 5°, the mixture was filtered to give 11 g (75%) of methylammonium iodide, m.p. 229–231°.

$C_{24}H_{30}INO_2$ (491.4) Calc. C 58.7 H 6.2 N 2.9% Found C 58.7 H 6.3 N 3.1%

To the above methylammonium iodide (9.8 g, 0.02 mol) in methanol (40 ml) was added 2N NaOH (80 ml), and the mixture was heated under reflux for 2 h then extracted with CH_2Cl_2. The extract was dried and evaporated. The residue was recrystallized from ether at −20°, giving 6.6 g (91%) of **22**, m.p. 137–139°. – ^{1}H-NMR.: 7.3–6.3 (*m*, 4 H arom.); 6.85 and 6.5 (2 *s*, H–C(2) and H–C(3)); 3.95 and 3.8 (2 *s*, 2 CH_3O); 2.1 (*s*, CH_3N).

$C_{24}H_{29}NO_2$ (363.5) Calc. C 79.3 H 8.0 N 3.9% Found C 79.2 H 8.2 N 4.0%

*6,7,8,9,10,17-Hexahydro-2,3-methoxy-7-methyl-11,17-methano-5*H*-dibenzo[*d,g*]azacyclotridecane* (**23**). To compound **19** (1.5 g, 4.3 mmol) in acetone (40 ml) was added methyl iodide (0.71 g, 5 mmol). The mixture was kept at RT. for one week, then filtered to give 2.05 g (97%) of methylammonium iodide, m.p. 209–218°. A part (1.5 g, 3 mmol) was dissolved in methanol (6 ml), 2N NaOH (12 ml) was added and the mixture was heated under reflux for 3 h, then diluted with H_2O (50 ml) and extracted with CH_2Cl_2. The extract was dried and evaporated. The residue was crystallized from ethanol (6 ml), giving 0.55 g (49.5%) of **25**, m.p. 114–116°. – ^{1}H-NMR. (90 MHz, DMSO at 120°): 7.05 (*m*, H–C(13), H–C(14), H–C(15) and H–C(16)); 6.75 and 6.65 (2 *s*, H–C(1) and H–C(4)); 6.25 (*s*, H–C(12)); 4.55 (*d*×*d*, $J=3$ and 5, H–C(17)); 3.8 and 3.7 (2 *s*, 2 CH_3O); 2.2 (*s*, CH_3N).

$C_{24}H_{28}NO_2$ (363.5) Calc. C 79.3 H 8.0 N 3.9% Found C 79.0 H 8.0 N 3.9%

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