Synthesis of Hexahydro-2-pyrindine (= Hexahydrocyclopenta[*c*]pyridine) Derivatives as Conformationally Restricted Analogs of the Nicotinic Ligands Arecolone and Isoarecolone

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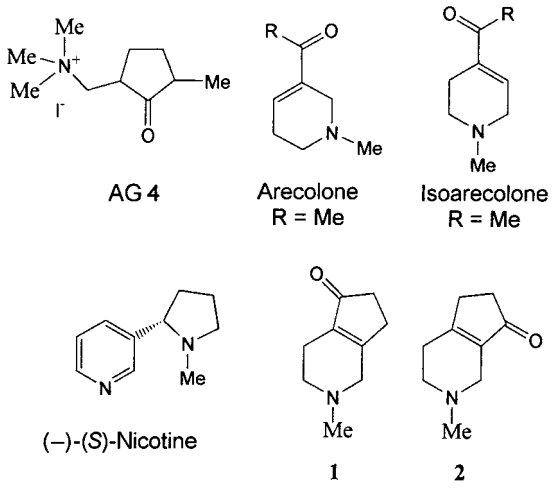
Two hexahydropyrindine derivatives, 1,2,3,4,6,7-hexahydro-2-methyl-5*H*-cyclopenta[*c*]pyridin-5-one (**1**) and 1,2,3,4,5,6-hexahydro-2-methyl-7*H*-cyclopenta[*c*]pyridin-7-one (**2**), and their methiodides **14** and **26**, respectively, were synthesized. They can be considered rigid analogues of the known nicotinic agonists arecolone (=1-(1,2,5,6-tetrahydro-1-methylpyridin-3-yl)ethanone) and isoarecolone (=1-(1,2,3,6-tetrahydro-1-methylpyridin-4-yl)ethanone). The affinity for the central nicotinic receptor were measured on rat cerebral cortex. Although only the methiodide **14**, among the four conformationally restricted compounds, shows an appreciable affinity, the results obtained provide useful information on the molecular requirements at the interaction site of the central nicotinic receptors.

Introduction. – The nicotinic receptor is the prototype of the family called ligand-gated ion channels (LGIC). Interest in the nicotinic receptor subtypes present in the central nervous system (nAChR) is steadily growing, since they play a role in many important physiological processes such as cognition, memory, and pain, and are involved in severe central nervous system pathologies, such as *Alzheimer*'s and *Parkinson*'s diseases, *Tourette*'s syndrome, and schizophrenia [1]. Therefore, selective nicotinic agonists, acting in the central nervous system and devoid of the side effects shown by nicotine, are, at present, good drug candidates for a variety of pathological conditions [2].

An H-bond acceptor group and a charged N-atom located a certain distance from each other, are considered critical for interaction with nicotinic receptors [3][4]. Classical nicotinic agonists belong to two main structural categories: pyridine derivatives (such as nicotine) and carbonyl derivatives. In the carbonyl class, both esters (such as acetylcholine) and α,β-unsaturated ketones, such as arecolone (=1-(1,2,5,6-tetrahydro-1-methylpyridin-3-yl)ethanone) and isoarecolone (=1-(1,2,3,6-tetrahydro-1-methylpyridin-4-yl)ethanone) [5][6], are found. The latter are two potent centrally acting nicotinic agonists derived from chemical manipulation of arecoline, a naturally occurring alkaloid extracted from the seeds of *Areca catechu* L. [7]. It has been shown that replacement of the Me group with small alkyl groups does not greatly affect activity, showing that some space is available in this region of the interaction site [6].

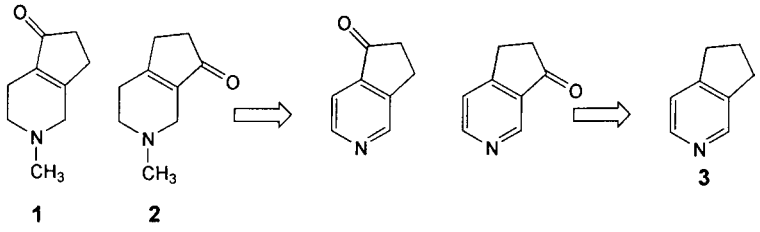
Some years ago, the synthesis and biological activity of AG 4 (= *N*,*N*,*N*,3-tetramethyl-2-oxocyclopentanemethanaminum iodide), a compound previously studied only on the peripheral nAChR, was reported [8]. This compound, which presents



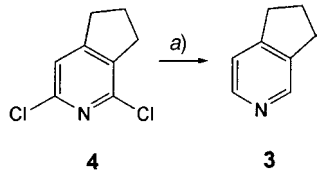
lower affinity for the central nAChR with respect to (−)-(*S*)-nicotine (= 3-[(2*S*)-1-methylpyrrolidin-2-yl]pyridine) (K_i values are 26 μM and 8 nM, resp.), nevertheless is able to produce an analgesic effect, after *i.c.v.* injection in mice, with higher efficacy than (−)-(*S*)-nicotine, even if it seems less potent [9]. However, AG 4 is useless as a drug, since it is a quaternary ammonium compound, and, aiming to improve its pharmacological and pharmacokinetics properties, compounds **1** and **2** were designed. These can be considered conformationally restricted analogs [10] of AG 4, where the cationic N-group is incorporated into a tetrahydropyridine ring. Compounds **1** and **2** can also be viewed as frozen analogs of isoarecolone and arecolone, respectively, and their study could give additional information on the topography of the active site of the receptor. In this paper, the synthesis and biological evaluation of compounds **1** and **2**, as well as that of their methiodides **14** and **26**, are reported.

Results. – *Chemistry.* A simple retrosynthetic analysis (*Scheme 1*) suggests the heterocycle **3** as a suitable starting material for our synthesis. Compound **3**, 6,7-dihydro-5*H*-cyclopenta[*c*]pyridine, can be found in both the *Chemical Abstracts* and *Beilstein* databases as 6,7-dihydro-5*H*-2-pyrindine, a name which we use in the *General Part*. In fact, **3** can be transformed into both of the desired compounds **1** and **2** by simple known methods [11][5]. *Prelog* and *Metzler* [12a] described the synthesis of **3** with a 30%

Scheme 1



Scheme 2



4 **3**

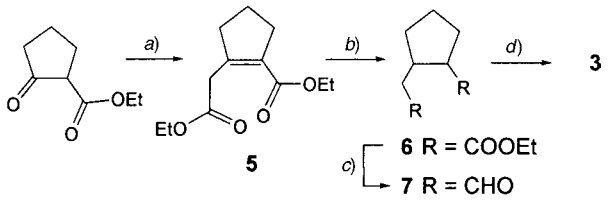
a) H_2, $PdCl_2$, MeCOONa.

yield, but *Ayerst* and *Schofield* [12b], by the same procedure, obtained much lower yields (4–11%). Later, *Cavill et al.* [13] worked on similar natural products. In our hands, the reported methods [12] afforded **3** in even lower overall yields (2%).

Since several steps were required to transform **3** into the final compounds **1** and **2**, considerable amounts of 6,7-dihydro-5*H*-2-pyrindine (**3**) were needed, and we tried to improve its preparation by designing different synthetic routes. Starting from the commercially available ethyl 2-oxocyclopentanecarboxylate and by reported procedures [14], 1,3-dichloro-6,7-dihydro-5*H*-2-pyrindine **4** was obtained and transformed into compound **3**, however, without any substantial improvement in the yields (*Scheme 2*).

In a second attempt (*Scheme 3*), addition of ethyl (tributylphosphoranyl)acetate [15] to the carbonyl group of ethyl 2-oxocyclopentanecarboxylate gave the unsaturated ester **5** [16], which was hydrogenated to **6** [17] and reduced to the dialdehyde **7** [18]. Unfortunately, **7** proved to be unstable: all attempts at chromatographic purification resulted in loss of product. Therefore, after the workup, the residue was immediately treated with hydroxylamine [19] to give the desired compound **3**. As a consequence, the overall yield of this process was low (5% at best) and, due to the instability of **7**, the procedure was not always reproducible.

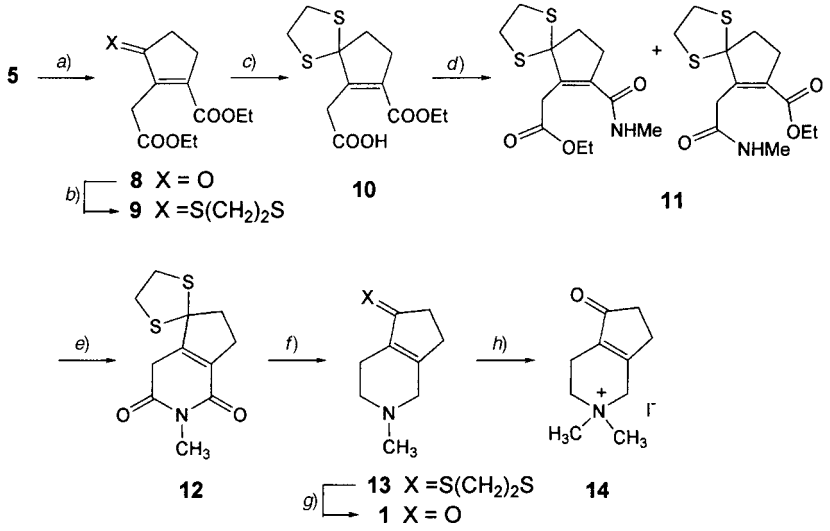
Scheme 3



a) $Bu_3PCHCOOEt$. *b*) H_2, Pd/C. *c*) Diisobutylaluminium hydride (DIBALH). *d*) $NH_2OH \cdot HCl$.

Therefore, we thought it wiser to switch to different synthetic pathways to implement the synthesis of the two isomers separately. Accordingly, compound **5** (*Scheme 4*) was oxidized at the allylic position, yielding ketone **8** [20], which was protected with ethane-1,2-dithiol to give **9**. Apparently, the hydrolysis of **9** with 1 equiv. of NaOH gave only one of the two possible acids, which was identified as **10**, since only the ester group at lower field had disappeared from the NMR spectrum. However, the following reaction with ethyl carbonochloridate and methylamine gave two isomeric amides **11** (in 65 : 35 ratio), which were not separated, since treatment with base yielded

Scheme 4

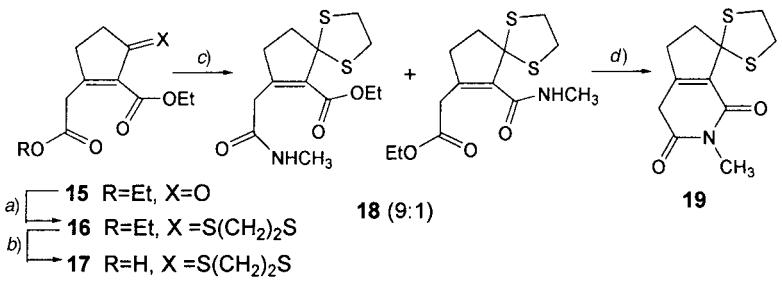


a) Pyridinium dichromate, *t*BuOOH. *b*) Ethane-1,2-dithiol. *c*) NaOH. *d*) ClCOOEt, $MeNH_2$. *e*) *t*BuOK. *f*) $LiAlH_4$. *g*) $Tl(NO_3)_3$. *h*) MeI.

the same dicarboximide **12**. Subsequent reduction with $LiAlH_4$ afforded the protected amine **13**. Deprotection of the carbonyl function was attempted in several ways (acid hydrolysis, Hg salts [21]), but only the method of *Smith* and *Hanna* [22] was effective. Compound **1** proved to be unstable as a free base and was transformed into the oxalate salt and the methiodide **14**.

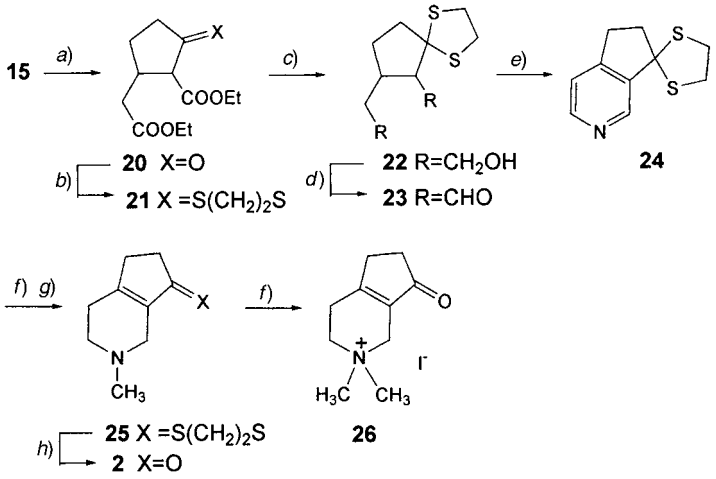
For the synthesis of compound **2**, the analogous synthetic pathway was first attempted (*Scheme 5*). Compound **15** [23] was prepared according to [24] and protected with ethane-1,2-dithiol to give **16**. Contrary to what happened with its isomer **9**, basic hydrolysis of **16** gave only traces of the desired acid **17**, which was instead obtained by acid hydrolysis; reaction with ethyl carbonochloridate and methylamine again gave two isomeric amides **18**, in a 9:1 ratio. Reaction with *t*BuOK then yielded

Scheme 5



a) Ethane-1,2-dithiol. *b*) HCl. *c*) ClCOOEt, $MeNH_2$. *d*) *t*BuOK.

Scheme 6



a) H_2,Pd/C. *b*) Ethane-1,2-dithiol. *c*) $LiAlH_4$. *d*) $(CF_3CO)_2O$, DMSO, Et_3N. *e*) $NH_2OH \cdot HCl$. *f*) MeI. *g*) $NaBH_4$. *h*) $Tl(NO_3)_3$.

the dicarboximide **19**. Unlike dicarboximide **12**, compound **19** proved to be unstable, and any attempt to reduce it to the corresponding amine failed. Therefore, we had to design a new synthetic pathway (*Scheme 6*), similar to that shown in *Scheme 3*, which involved the synthesis of a pyrindine intermediate. The diester **15** was hydrogenated to **20** [25] and protected in the usual way to give **21**. The dialdehyde **23**, obtained by reduction of **21** to the dialcohol **22** and subsequent oxidation, was immediately reacted with hydroxylamine to give the protected pyrindinone **24**, which was transformed into **25** by reaction with MeI and subsequent reduction with $NaBH_4$. Deprotection of the carbonyl function gave then compound **2** which, like its isomer **1**, was unstable as a free base and was thus transformed into the oxalate salt and into the methiodide **26**.

Pharmacology. Compounds **1** and **2** (as oxalates) and methiodides **14** and **26** were tested *in vitro* on rat brain homogenates to evaluate their affinity for the central nicotinic receptors labeled by [^{3}H]cytisine, that is believed to label $\alpha_4\beta_2$ which represents up to 90% of the high-affinity agonist binding sites in rat brain [26][27]. Their binding affinity is reported in *Table 1*, together with those of the compounds reported in the *Introduction*.

Discussion. – The data reported in *Table 1* show that, among the new compounds, only the methiodide **14** possesses some modest affinity for the central nicotinic receptor as **1**, **2**, and **26** do not displace [^{3}H]cytisine from rat cerebral cortex up to a 100 μM concentration. Compared to AG 4, the incorporation of the cationic side chain into a six-membered ring resulted in a 6-fold increase of affinity for compound **14** and in complete loss of affinity for **26**. Surprisingly, freezing the acetyl moiety of arecolone and isoarecolone into a five-membered ring (compounds **1** and **2**) resulted in a complete loss of affinity, showing that to maintain nicotinic receptor affinity, no restriction of the conformational freedom of that function is allowed. A reasonable explanation for this

Table 1. *Binding Affinity of the Synthesized and Reference Compounds*

	AG 4	Isoarecolone	Arecolone	Nicotine	**1**	**2**	**14**	**26**
K_i/μM[a])	26 ± 1.4[b])	0.048 ± 0.0022[c])	0.033 ± 0.0055[c])	0.0082 ± 0.0005[b])	> 10	> 10	4.2 ± 0.058	> 10

[a]) On rat brain homogenates. The nicotinic receptors were labeled by [^{3}H]cytisine. See [9] for the exper. protocol. [b]) See [9]. [c]) See [6].

result can be found by looking at the conformational and steric characteristics of the two molecules with respect to the parent compounds.

A tenet of the frozen-analog approach is that, to maintain maximum affinity, the parent compound has to be constrained into a biologically active conformation, and the additional volume of the moiety used to reduce conformational freedom must be compatible with the space available at the interaction site [10]. Therefore, a conformational analysis of the lead compounds and of the rigid analogs is required to understand the reasons for the inactivity.

In the case of arecolone and isoarecolone, two stable conformations are possible, with the enone moiety in a s-*cis* or s-*trans* arrangement (*Table 2*), which can be converted to each other at a small energy cost (*Fig. 1*). *Ab initio* calculations predict a planar disposition of the enone group, while semiempirical methods predict a deviation from planarity. Both methods show that the s-*trans* conformer is more stable than the s-*cis* one. The distance between the N-atom (charged group) and the O-atom (H-bond-acceptor group) is a feature thought to be critical for interaction with the nicotinic receptor [3][4]: the two conformations of isoarecolone do not differ in this respect while, in the case of arecolone, the s-*trans* conformer shows a shorter distance (4.2 Å) with respect to the s-*cis* one (4.8 Å).

The conformational characteristics of compounds **1** and **2** are also reported in *Table 2*. Both molecules represent the rigid analogs of the s-*trans* (more stable) conformation of the lead compounds: in case of **1**, the N ··· O distance is very close to that of isoarecolone, while the N ··· O distance of **2** is intermediate between those of the

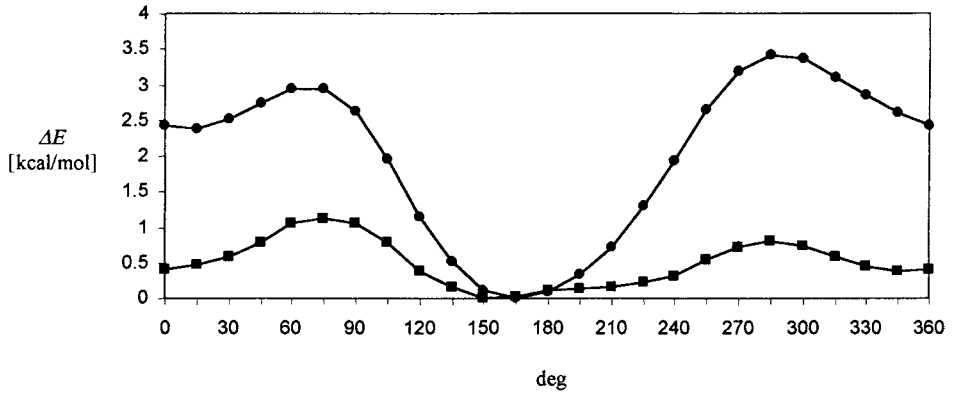


Fig. 1. *Dihedral driver calculation for arecolone* (●) *and isoarecolone* (■). The dihedral angle is defined as C=C–C=O.

Table 2. *Results of* ab initio *and Semiempirical Calculations*

	ΔE [kcalmol^{-1}]		N–O distance [Å]		Dihedral angle O=C–C=C [°]	
	ab initio	AM1	*ab initio*	AM1	*ab initio*	AM1
Isoarecolone	2.7	0.4	5.0	5.1	2	8
	0	0	4.9	5.1	178	155
Arecolone	5.8	2.4	4.8	4.8	4	11
	0	0	4.1	4.2	–179	164
1	–	–	5.1	5.2	180	179
2	–	–	4.4	4.5	178	180
14	–	–	5.1	5.2	180	180
26	–	–	4.4	4.5	178	180

two conformers of arecolone and close to that of other classic nicotinic agonists such as anatoxin [2][28]. Therefore, this feature alone does not account for the loss of affinity.

In *Fig. 2*,*a*, the superimposition of both conformations of arecolone (s-*cis* and s-*trans*) and isoarecolone (s-*cis* and s-*trans*) is reported. While the two conformations of isoarecolone coincide, those of arecolone are different: the best fit is obtained with the s-*cis* conformation, which overlaps isoarecolone with a lower r.m.s. value (0.11) with respect to the s-*trans* one (0.39). The tetrahydropyridine ring occupies a volume similar to that occupied by isoarecolone. Compound **2** (*Fig. 2*,*b*) overlaps perfectly with s-*trans*-arecolone, which is obviously not the active conformation, since **2** is completely inactive. Therefore, a reasonable explanation for the lack of affinity of compounds **1** and **2** appears to be the extra volume occupied by the CH_2CH_2 part of the tetrahydropyridine ring, which lies in an area probably occupied by the receptor. Even if the analogs **1** and **2** differ from the lead by only one additional CH_2 group, the conformational constraint of the ring puts it in a region that prevents an efficient fitting to the receptor.

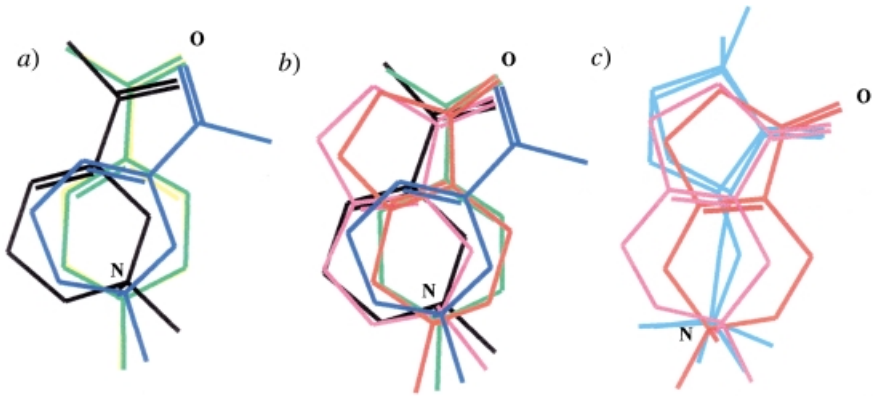


Fig. 2. a) *Overlap of isoarecolone and arecolone* (yellow, s-*cis*-isoarecolone; green, s-*trans*-isoarecolone; black, s-*trans*-*arecolone; blue, s-cis*-arecolone). b) *Overlap of compounds* **1** *and* **2**, *isoarecolone, and arecolone* (green, s-*trans*-isoarecolone; black, s-*trans*-arecolone; blue, s-*cis*-arecolone; red, compound **1**; magenta, compound **2**). c) *Overlap of AG 4 and compounds* **14** *and* **26** (cyano, s-*cis*- and s-*trans* AG 4 [8]; red, compound **14**; magenta, compound **26**).

As far as the methiodides are concerned, in *Fig. 2,c*, the overlap of **14** and **26** with AG 4 is shown. The lack of affinity of **26** can be explained as above. The fact that, contrary to the tertiary amine **1**, methiodide **14** shows some affinity may depend on a different mode of interaction with the receptor, due to the presence of the quaternary ammonium group, which is characterized by a different volume and charge distribution [29].

In conclusion, the reduction of conformational flexibility of our leads produced different results. The nicotinic affinity of AG 4 was slightly improved in **14**, but the affinity of arecolone and isoarecolone was completely abolished in compounds **1** and **2**. Of course, our efforts to develop new centrally active nicotinic agonists have been frustrated, as **1** and **2** do not show any affinity for the nicotinic receptors, while **14** is still a quaternary ammonium compound and, as a consequence, will not cross the blood-brain barrier. Nevertheless, the results obtained have provided information that may cast further light on the molecular requirements of central nicotinic receptors.

Experimental Part

General. All reagents and solvents were purchased from commercial suppliers and used without further purification with the following exceptions: anh. THF was distilled from Na/benzophenone, and toluene from Na wire. Yields are given after purification, unless otherwise stated. Column chromatography (CC): silica gel *40* (0.063–0.200 mm; *Merck*). Flash chromatography (FC): silica gel *40* (0.040–0.063 mm, *Merck*). M.p.: *Büchi* apparatus; uncorrected. IR Spectra: *Perkin-Elmer-681* spectrophotometer; nujol mull for solids and neat for liquids; in cm^{-1}. NMR Spectra: δ in ppm J in Hz. *Gemini-200* spectrometer. Mass spectra: *Carlo-Erba QMD-1000* spectrometer. HR-MS: *VG-70-250S* (*VG Analytical Ltd*., Manchester, UK) double-focus mass spectrometer; resolution 5000.

*6,7-Dihydro-5*H*-cyclopenta[*c*]pyridine* (**3**) [12]. *Method A* (*Scheme 2*). A mixture of 1,3-dichloro-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine (**4**) [11] (1.65 g, 9 mmol), MeCOONa (1.5 g, 18 mmol) and $PdCl_2$ (0.15 g) in abs. EtOH (20 ml) was hydrogenated in a *Parr* apparatus at 48 psi for 20 h. After filtration and evaporation, the residue was treated with $NaHCO_3$ soln. and extracted with $CHCl_3$. The extract was dried and evaporated: 57% of **3**. Overall yield, starting from the commercially available ethyl 2-oxocyclopentanecarboxylate, 1%.

Method B (*Scheme 3*): A mixture of crude **7** [18] (1.8 g, 0.0129 mol) and $NH_2OH \cdot HCl$ (2.7 g, 0.039 mol) in glacial MeCOOH (30 ml) was kept under reflux for 4 h. After evaporation, the residue was treated with $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried and evaporated and the residue purified by CC: 26% (from **6**) of **3**. ^{1}H-NMR ($CDCl_3$): 2.01–2.19 (*m*, $CH_2CH_2CH_2$); 2.86–2.99 (*m*, $CH_2CH_2CH_2$); 7.16 (*d*, $J = 5.0$, 1 arom. H); 8.34 (*d*, $J = 5.0$, 1 arom. H); 8.46 (*s*, 1 arom. H).

Ethyl 2-(Ethoxycarbonyl)cyclopent-1-ene-1-acetate (**5**) [16]. A mixture of ethyl 2-oxocyclopentanecarboxylate (18 ml, 19 g, 0.12 mol) and ethyl (tributylphosphoranyl)acetate [15] (35 g, 0.12 mol) in toluene (20 ml) was kept under reflux for 5 h. After evaporation, the unreacted ketone was distilled off under vacuum and the residue submitted to FC (cyclohexane/AcOEt 7:3): 69% of **5**. Oil. B.p. 120°/2 Torr ([16]: 155°/20 Torr). ^{1}H-NMR ($CDCl_3$): 1.26 (*t*, $J = 7.0$, 1 Me); 1.28 (*t*, $J = 7.0$, 1 Me); 1.78–1.95 (*m*, $CH_2CH_2CH_2$); 2.52–2.72 (*m*, $CH_2CH_2CH_2$); 3.68 (*s*, CH_2CO); 4.15 (*q*, $J = 7.0$, 1 CH_2O); 4.18 (*q*, $J = 7.0$, 1 CH_2O). MS: 226 (1, M^+), 180 (100), 152 (91), 134 (73), 124 (40), 79 (80).

Ethyl 2-(Ethoxycarbonyl)cyclopentaneacetate (**6**) [17]. A soln. of **5** (1.2 g) in abs. EtOH (20 ml) was hydrogenated in a *Parr* apparatus at 20 psi over 10% Pd/C (0.1 g) overnight. Filtration and evaporation gave 92% of **6**. ^{1}H-NMR ($CDCl_3$): 1.25 (*t*, $J = 7.2$, 2 Me); 1.61–2.08 (*m*, 6 H); 2.23–2.64 (*m*, 4 H); 4.11 (*q*, 1 CH_2O); 4.13 (*q*, $J = 7.2$, 1 CH_2O).

2-Formylcyclopentaneacetaldehyde (**7**) [18]. To a soln. of **6** (0.56 g, 2.5 mmol) in anh. toluene (20 ml), kept at −90°, 1.5M DIBALH in toluene (3.33 ml, 2 equiv.) was added, and the mixture was stirred at low temp. for 4 h. The reaction was quenched with ice, and the mixture was allowed to reach r.t. The aq. layer was washed with $CHCl_3$ and the combined org. phase dried and evaporated: crude **7**. ^{1}H-NMR ($CDCl_3$): 9.64 (*d*, $J = 2.9$, 1 CHO); 9.76 (*s*, 1 CHO).

Any attempt to purify crude **7** by CC failed, and the product was treated as such in the following step.

Ethyl 2-(Ethoxycarbonyl)-5-oxocyclopent-1-ene-1-acetate (**8**) [20]. A suspension of **5** (6.9 g, 0.03 mol), *Celite* (25 g), and pyridinium dichromate (52.7 g, 0.14 mol) in benzene (200 ml) was kept at 0°, and 70% ^{t}BuOOH/H_2O (12.4 g, 0.137 mol) was added. The mixture was vigorously stirred at r.t. for 17 h, then it was diluted with Et_2O, the solid material filtered off, and the filtrate evaporated. The residue was submitted to FC (cyclohexane/AcOEt 8:2): **5** (2.1 g) and **8** (2.9 g). **8**: Oil. ^{1}H-NMR ($CDCl_3$): 1.25 (*t*, *J* = 7.2, 1 Me); 1.34 (*t*, *J* = 7.2, 1 Me); 2.50–2.58 (*m*, 1 CH_2); 2.81–2.89 (*m*, 1 CH_2); 3.61 (*s*, CH_2CO); 4.14 (*q*, *J* = 7.2, 1 CH_2O); 4.30 (*q*, *J* = 7.2, 1 CH_2O). ^{13}C-NMR ($CDCl_3$): 14.49 (*q*); 27.13 (*t*); 29.99 (*t*); 34.28 (*t*); 61.43 (*t*); 61.87 (*t*); 143.79 (*s*); 158.01 (*s*); 165.03 (*s*); 169.80 (*s*); 208.44 (*s*).

Ethyl 7-(Ethoxycarbonyl)-1,4-dithiaspironon-6-ene-6-acetate (**9**). A mixture of **8** (2.2 g, 0.009 mol), ethane-1,2-dithiol (1.48 ml, 1.66 g, 0.018 mol), and TsOH (0.30 g) in anh. toluene was kept under reflux for 3 h (*Stark* trap). The mixture was then treated with 5% $NaHCO_3$ soln., the org. phase dried (Na_2SO_4) and evaporated, and the residue purified by FC (cyclohexane/AcOEt 5:5): 2.4 g (83%) of **9**. Oil. IR: 1740 (CO), 1710 (CO). ^{1}H-NMR ($CDCl_3$): 1.26 (*t*, *J* = 7.0, 1 Me); 1.28 (*t*, *J* = 7.0, 1 Me); 2.48–2.58 (*m*, 1 CH_2); 2.63–2.72 (*m*, 1 CH_2); 3.23 (*s*, 2 CH_2S); 3.64 (*s*, CH_2CO); 4.14 (*q*, *J* = 7.0, 1 CH_2O); 4.18 (*q*, *J* = 7.0, 1 CH_2O). ^{13}C-NMR ($CDCl_3$): 14.62 (*q*); 31.40 (*t*); 33.48 (*t*); 41.18 (*t*); 44.97 (*t*); 60.83 (*t*); 61.18 (*t*); 79.06 (*s*); 133.18 (*s*); 149.49 (*s*); 165.13 (*s*); 170.78 (*s*). Anal. calc. for $C_{14}H_{20}O_4S_2$: C 53.14, H 6.37; found: C 53.34, H 6.48.

*1,2,3,4,6,7-Hexahydro-2-methylspiro[5*H*-cyclopenta[*c*]pyridine-5,2′-[1,3]dithiolane]-1,3-dione* (**12**). A soln. of **9** (0.5 g, 0.0016 mol) and NaOH (0.064 g, 0.0016 mol) in EtOH/H_2O 10:1 was stirred at r.t. for 24 h. The solvent was then removed and the residue partitioned between H_2O and Et_2O. The org. phase was dried (Na_2SO_4) and evaporated, to give 0.17 g of unreacted **9**. The aq. phase was acidified to pH 3 with dil. HCl soln. and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and evaporated: 0.25 g of **10**. ^{1}H-NMR ($CDCl_3$): 1.27 (*t*, *J* = 7.0, Me); 2.52–2.60 (*m*, 1 CH_2); 2.65–2.75 (*m*, 1 CH_2); 3.34 (*s*, 2 CH_2S); 3.66 (*s*, CH_2CO); 4.17 (*q*, *J* = 7.0, CH_2O).

To a soln. of crude **10** in $CHCl_3$ stabilized with amylene (15 ml), kept at 0°, Et_3N (0.2 ml) and ethyl carbonochloridate (0.13 ml, 1.3 equiv.) were added. After 1 h at 0°, 5M $MeNH_2$ in toluene (1.5 ml) was added, and the mixture was allowed to warm to r.t. The mixture was treated with H_2O and extracted with $CHCl_3$. The extract was dried and evaporated: 0.25 g of crude **11**. Pale yellow oil. IR: 3337 (NH), 1728 (COO), 1655, 1629 (CON). ^{1}H-NMR ($CDCl_3$): 1.18–1.38 (*m*, *Me*CH_2O); 2.50–2.74 (*m*, 2 CH_2); 2.79 (*d*, *J* = 4.0, 35%) and 2.85 (*d*, *J* = 4.0, 65%) (MeN); 3.20–3.36 (*m*, 2 CH_2S); 3.41 (*s*, CH_2CO); 4.05–4.35 (*m*, MeCH_2O); 7.4 (br. *s*, NH).

Crude **11** was dissolved in anh. dimethoxyethane, and ^{t}BuOK (0.1 g, 1.1 equiv.) was added under N_2. After 2 h stirring at r.t., the solvent was evaporated and the residue treated with dil. HCl soln. and extracted with $CHCl_3$. The extract was dried and evaporated: 0.2 g (50% from **9**) of **12**. M.p. 92–93°. IR: 3330 (br.), 1720, 1659. ^{1}H-NMR ($CDCl_3$): 2.65–2.72 (*m*, CH_2CH_2); 3.22 (*s*, MeN); 3.32–3.43 (*m*, 2 CH_2S); 3.62–3.68 (*m*, CH_2CO). ^{13}C-NMR ($CDCl_3$): 28.2 (*q*); 30.3 (*t*); 34.1 (*t*); 43.6 (*t*); 45.8 (*t*); 76.1 (*s*); 131.7 (*s*); 155.5 (*s*); 165.8 (*s*); 173.1 (*s*). MS: 255 (100, M^+), 227 (87), 195 (50), 194 (92), 162 (91), 110 (45), 61 (65). Anal. calc. for $C_{11}H_{13}NO_2S_2$: C 51.74, H 5.13, N 5.49; found: C 51.57, H 5.25, N 5.31.

*1,2,3,4,6,7-Hexahydro-2-methylspiro[5*H*-cyclopenta[*c*]pyridine-5,2′-[1,3]dithiolane]* (**13**). A suspension of $LiAlH_4$ (0.37 g, 0.01 mol) in anh. 1,2-dimethoxyethane (20 ml) was heated under reflux under N_2, and a soln. of **12** (0.9 g, 0.0035 mol) in anh. (10 ml) 1,2-dimethoxyethane was added dropwise. The suspension was heated for a further 5 h. After evaporation, the residue was treated with dil. HCl soln. and extracted with $CHCl_3$. The aq. layer was alkalinized and extracted again with $CHCl_3$. The org. phase was dried and evaporated and the residue separated by CC (abs. EtOH/petroleum ether/Et_2O/$CHCl_3$/NH_4OH 40:500:200:200:2.5): 20% of **13**. M.p. 43–47°. ^{1}H-NMR ($CDCl_3$): 2.23–2.41 (*m*, 4 H); 2.39 (*s*, MeN); 2.54–2.64 (*m*, 4 H); 2.88–2.94 (*m*, 1 CH_2N); 3.30 (*s*, 2 CH_2S). ^{13}C-NMR ($CDCl_3$): 23.1 (*t*); 32.3 (*t*); 41.2 (*t*); 45.8 (*q*); 46.2 (*t*); 52.5 (*t*); 55.9 (*t*); 76.3 (*s*); 135.5 (*s*); 136.2 (*s*). MS: 227 (8, M^+), 207 (8), 166 (22), 156 (12), 134 (14), 109 (100), 91 (13). Anal. calc. for $C_{11}H_{17}NS_2$: C 58.10, H 7.54, N 6.16; found: C 57.96, H 7.59, N 6.32.

*1,2,3,4,6,7-Hexahydro-2-methyl-5*H*-cyclopenta[*c*]pyridin-5-one* (**1**). To a soln. of **13** (0.06 g, 0.26 mmol) in MeOH (5 ml) and THF (1 ml), a soln. of $Tl(NO_3)_3 \cdot 3\,H_2O$ (0.22 g, 0.49 mmol) in MeOH (2 ml) was added. After stirring for 3 h at r.t., the mixture was diluted with CH_2Cl_2 and the solid material filtered off. The solvent was removed, and the residue treated with H_2O and CH_2Cl_2. The aq. layer was alkalinized and extracted with $CHCl_3$. The extract was dried and evaporated: 0.03 g (75%) of **1**. Oil. IR: 1700, 1650. MS: 151 (80, M^+), 150 (56), 123 (100), 122 (59), 108 (76), 94 (38), 79 (71). ^{1}H-NMR ($CDCl_3$): 2.23–2.34 (*m*, 2 H); 2.45 (*s*, MeN); 2.38–2.64 (*m*, 6 H); 3.23 (*s*, 1 CH_2N). ^{13}C-NMR ($CDCl_3$): 21.5 (*t*); 30.1 (*t*); 35.0 (*t*); 45.8 (*q*); 51.8 (*t*); 57.2 (*t*); 137.2 (*s*); 170.6 (*s*); 207.9 (*s*).

On standing, tarry materials were formed from **1**. Thus, **1** was immediately transformed into the oxalate salt, which, however, is so hygroscopic that no m.p. was determined. HR-MS: 151.09980 (calc. 151.09971).

*2,3,4,5,6,7-Hexahydro-2,2-dimethyl-5-oxo-1*H*-cyclopenta[*c*]pyridinium Iodide* (**14**). To a soln. of **1** (0.04 g, 0.3 mmol) in anh. Et_2O (10 ml), an excess of MeI was added. After stirring at r.t. in the dark for 24 h, the solid was collected and dried. ^{1}H-NMR (D_2O): 2.42–2.62 (*m*, 3 CH_2); 3.07 (*s*, 2 MeN); 3.44–3.50 (*m*, 1 CH_2N); 4.25 (*s*, 1 CH_2N). ^{13}C-NMR (CD_3OD): 16.6 (*t*); 27.0 (*t*); 33.9 (*t*); 51.6 (*q*); 59.0 (*t*); 62.8 (*t*); 133.5 (*s*); 162.4 (*s*); 206.3 (*s*). Anal. calc. for $C_{10}H_{16}INO$: C 40.97, H 5.50, N 4.78; found: C 41.15, H 5.71, N 4.91.

Ethyl 2-(Ethoxycarbonyl)-3-oxocyclopent-1-ene-1-acetate (**15**) [23] was prepared according to [24], starting from potassium ethyl malonate (instead of potassium methyl malonate). Diethyl 3,6-dioxooctanedioate was obtained in 91% yield (^{1}H-NMR ($CDCl_3$): 1.28 (*t*, *J* = 7.3, 2 Me); 2.86 (*s*, $COCH_2CH_2CO$); 3.49 (*s*, 2 $COCH_2$-CO); 4.19 (*q*, *J* = 7.3, 2 CH_2O)). This intermediate was treated with NaOH as described in the literature to give **15** (quant.). ^{1}H-NMR ($CDCl_3$): 1.27 (*t*, *J* = 7.3, 1 Me); 1.33 (*t*, *J* = 7.3, 1 Me); 2.48–2.59 (*m*, 1 CH_2); 2.73–2.81 (*m*, 1 CH_2); 3.82 (*s*, 1 CH_2); 4.18 (*q*, *J* = 7.3, 1 CH_2O); 4.30 (*q*, *J* = 7.3, 1 CH_2O). ^{13}C-NMR ($CDCl_3$): 14.58 (*q*); 31.62 (*t*); 35.48 (*t*); 38.38 (*t*); 61.43 (*t*); 61.91 (*t*); 134.65 (*s*); 162.90 (*s*); 168.45 (*s*); 178.39 (*s*); 203.19 (*s*).

Ethyl 6-(Ethoxycarbonyl)-1,4-dithiaspironon-6-ene-7-acetate (**16**). As described for **9**, from **15** (3.6 g): 2.27 g (48%) **16**; after purification by FC. IR: 1740 (CO), 1710 (CO). 1640 (C=C). ^{1}H-NMR ($CDCl_3$): 1.26 (*t*, *J* = 7.3, 1 Me); 1.32 (*t*, *J* = 7.3, 1 Me); 2.49–2.56 (*m*, CH_2CH_2); 3.24–3.39 (*m*, 1 CH_2S); 3.46–3.52 (*m*, 1 CH_2S); 3.56 (*s*, CH_2CO); 4.12 (*q*, *J* = 7.3, 1 CH_2O); 4.26 (*q*, *J* = 7.3, 1 CH_2O). ^{13}C-NMR ($CDCl_3$): 14.60 (*q*); 36.55 (*t*); 37.12 (*t*); 41.75 (*t*); 45.80 (*t*); 60.72 (*t*); 61.31 (*t*); 74.20 (*s*); 135.18 (*s*); 150.46 (*s*); 164.21 (*s*); 169.85 (*s*). Anal. calc. for $C_{14}H_{20}O_4S_2$: C 53.14, H 6.37; found: C 52.97, H 6.21.

*1,2,3,4,5,6-Hexahydro-2-methylspiro[7*H*-cyclopenta[*c*]pyridine-7,2′-[1,3]dithiolane]-1,3-dione* (**19**). A soln. of **16** (1.47 g) in EtOH (22 ml) and 2N HCl (7 ml) was kept at 80° for 4 h. After evaporation, the residue was treated with $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried and evaporated: 1.1 g (75%) of **16**. The aq. layer was acidified and extracted with $CHCl_3$ and the extract dried and evaporated: 0.26 g (19%) of **17**. ^{1}H-NMR ($CDCl_3$): 1.34 (*t*, *J* = 7.3, Me); 2.49–2.67 (*m*, CH_2CH_2); 3.35–3.41 (*m*, 1 CH_2S); 3.46–3.58 (*m*, 1 CH_2S); 3.56 (*s*, CH_2CO); 4.30 (*q*, *J* = 7.3, CH_2O). ^{13}C-NMR ($CDCl_3$): 14.58 (*q*); 36.63 (*t*); 37.40 (*t*); 41.80 (*t*); 45.94(*t*); 61.34 (*t*); 73.92 (*s*); 135.78 (*s*); 150.33 (*s*); 165.10 (*s*); 174.40 (*s*).

As described for **11**, **17** (0.26 g) gave 0.24 g of the two isomeric amides **18** (9:1 ratio). ^{1}H-NMR ($CDCl_3$): 1.19 (*t*, *J* = 7.4, 10%) and 1.32 (*t*, *J* = 7.4, 90%) (*Me*CH_2O); 2.46–2.68 (*m*, CH_2CH_2); 2.74 (*d*, *J* = 4.7, 90%) and 2.88 (*d*, *J* = 4.7, 10%) (MeN); 3.22–3.56 (*m*, 2 CH_2S); 3.30 (*s*, CH_2CO); 4.06 (*q*, *J* = 7.4, 10%) and 4.26 (*q*, *J* = 7.4, 90%) (MeCH_2O). ^{13}C-NMR ($CDCl_3$): 14.64 (*q*); 26.91 (*q*); 36.23 (*t*); 40.15 (*t*); 41.73 (*t*); 46.37 (*t*); 61.29 (*t*); 73.96 (*s*); 134.40 (*s*); 154.01 (*s*); 165.77 (*s*); 169.40 (*s*).

As described for **12**, **18** (0.11 g) gave **19** (0.09 g). Low-melting solid. ^{1}H-NMR ($CDCl_3$): 2.55–2.87 (*m*, CH_2CH_2); 3.20 (*s*, MeN); 3.30–3.52 (*m*, 1 CH_2S); 3.43 (*s*, CH_2CO); 3.64–3.81 (*m*, 1 CH_2S).

Compound **19** was unstable: the ^{1}H-NMR spectrum became progressively more complicated, with the increase of a *s* at 5.92 ppm. The GC/MS analysis showed only the presence of compounds with molecular mass (375) higher than that of **19** (255).

Ethyl 2-(Ethoxycarbonyl)-3-oxocyclopentaneacetate (**20**). A soln. of **15** (1 g) in abs. EtOH (30 ml) was hydrogenated over Pd/C (0.16 g) at 55 psi. Filtration and evaporation gave 0.94 g (93%) of **20**. Oil. ^{1}H-NMR ($CDCl_3$): 1.20 (*t*, *J* = 7.3, 1 Me); 1.26 (*t*, *J* = 7.3, 1 Me); 1.43–1.62 (*m*, 1 H); 2.21–2.61 (*m*, 5 H); 2.93 (*d*, *J* = 4, CH_2COO); 4.10 (*q*, *J* = 7.3, 1 CH_2O); 4.14 (*q*, *J* = 7.3, 1 CH_2O). ^{13}C-NMR ($CDCl_3$): 14.54 (*q*); 27.42 (*t*); 37.82 (*d*); 38.60 (*t*); 38.96 (*t*); 60.96 (*t*); 61.03 (*d*); 61.80 (*t*); 168.96 (*s*); 171.65 (*s*); 210.93 (*s*).

Ethyl 6-(Ethoxycarbonyl)-1,4-dithiaspirononane-7-acetate (**21**). As described for **9**: 75% of **21**. IR: 1740 (CO), 1730 (CO). ^{1}H-NMR ($CDCl_3$): 1.21 (*t*, *J* = 7.0, 1 Me); 1.26 (*t*, *J* = 7.0, 1 Me); 1.31–1.55 (*m*, 1 H); 2.01–2.26 (*m*, 2 H); 2.28–2.53 (*m*, 3 H); 2.70–2.98 (*m*, 2 H); 3.19–3.33 (*m*, 4 H); 4.08 (*q*, *J* = 7.0, 1 CH_2O); 4.14 (*q*, *J* = 7.0, 1 CH_2O). ^{13}C-NMR ($CDCl_3$): 14.62 (*q*); 14.73 (*q*); 32.24 (*t*); 39.38 (*d*); 39.56 (*t*); 40.09 (*t*); 40.54 (*t*); 44.52 (*t*); 60.81 (*t*); 61.09 (*t*); 64.75 (*d*); 73.05 (*s*); 172.29 (*s*); 172.69 (*s*). MS: 318 (22, M^+), 227 (33), 141 (50), 131 (100). Anal. calc. for $C_{14}H_{22}O_4S_2$: C 52.80, H 6.96; found: C 52.58, H 6.88.

6-(Hydroxymethyl)-1,4-dithiaspirononane-7-ethanol (**22**). To a soln. of **21** (1.6 g, 5 mmol) in anh. Et_2O (20 ml) under N_2, $LiAlH_4$ (0.64 g) was added portionwise. The mixture was heated under reflux for 3 h. After cooling, the mixture was treated with ice and extracted with Et_2O. The org. layer was dried and evaporated: 1.10 g (93%) of **22**. Solid. M.p. 72–73°. IR: 3360 (OH). ^{1}H-NMR ($CDCl_3$): 1.12–2.21 (*m*, 8 H); 3.19–3.36 (*m*, 2 CH_2S); 3.52–3.88 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$): 30.91 (*t*); 37.72 (*d*); 38.89 (*t*); 39.05 (*t*); 39.82 (*t*); 45.83 (*t*); 57.30 (*d*); 61.41 (*t*); 64.07 (*t*); 74.31 (*s*). Anal. calc. for $C_{10}H_{18}O_2S_2$: C 51.24, H 7.74; found: C 51.42, H 7.59.

*5,6-Dihydrospiro[7*H*-cyclopenta[*c*]pyridine-7,2′-[1,3]dithiolane]* (**24**). A mixture of DMSO (1 ml, 0.014 mol) and anh. CH_2Cl_2 (8 ml) was cooled to −50°. Then $(CF_3CO)_2O$ (2.02 g, 0.01 mol) was added. After 20 min at −50°, **22** (0.75 g, 0.0032 mol) in CH_2Cl_2 (7 ml) was added slowly. After 2 h stirring at −50°, the mixture was treated with Et_3N and allowed to warm to r.t. After evaporation, the residue was partitioned between H_2O

and Et_2O. The org. layer was dried and evaporated, giving 1.10 g of a residue containing *6-formyl-1,4-dithiospirononane-7-acetaldehyde* (**23**). Since all attempts to purify this mixture failed, the residue was used immediately in the next step. ^{1}H-NMR: 9.71, 9.78 (2 CHO); no trace of CH_2OH.

To the residue in MeCOOH (80 ml), $NH_2OH \cdot HCl$ (1.07 g) was added and the mixture heated under reflux for 1.5 h. After evaporation, the residue was treated with H_2O and the soln. made alkaline with 10% NaOH soln. and extracted with $CHCl_3$. The extract was dried and evaporated and the residue purified by FC ($CHCl_3$/MeOH 97:3): 0.31 g (46% from **22**) of **24**. ^{1}H-NMR ($CDCl_3$): 2.68 (*t*, *J* = 6.6, 2 H); 2.97 (*t*, *J* = 6.6, 2 H); 3.39–3.62 (*m*, 2 CH_2S); 7.14 (*d*, *J* = 5.2, 1 arom. H); 8.41 (*d*, *J* = 5.2, 1 arom. H); 8.73 (*s*, 1 arom. H). ^{13}C-NMR ($CDCl_3$): 31.26 (*t*); 41.45 (*t*); 47.54 (*t*); 70.79 (*s*); 120.03 (*d*); 142.81 (*s*); 146.84 (*d*); 148.60 (*d*); 151.86 (*s*). MS: 209 (32, M^+), 181 (100), 149 (52), 148 (64), 116 (56), 89 (18). Anal. calc. for $C_{10}H_{11}NS_2$: C 57.38, H 5.30, N 6.69; found: C 57.49, H 5.41, N 6.53.

*1,2,3,4,5,6-Hexahydro-2-methylspiro[7*H*-cyclopenta[*c*]pyridine-7,2′-[1,3]dithiolane]* (**25**). To a soln. of **24** (0.3 g) in $CHCl_3$ (50 ml), an excess of MeI was added. The mixture was kept under stirring at r.t. in the dark for 20 h. Evaporation gave *5,6-dihydro-2-methylspiro[7*H*-cyclopenta[c]pyridinium-7,2′-[1,3]dithiolane] iodide* (0.44 g, 88%). ^{1}H-NMR ($CDCl_3$): 2.86 (*t*, *J* = 7.1, 2 H); 3.09 (*t*, *J* = 7.1, 2 H); 3.46–3.62 (*m*, 1 CH_2S); 3.78–3.95 (*m*, 1 CH_2S); 4.72 (*s*, MeN); 7.92 (*d*, *J* = 7, 1 arom. H); 9.13 (*d*, *J* = 7, 1 arom. H); 9.19 (*s*, 1 arom. H). ^{13}C-NMR ($CDCl_3$): 32.88 (*t*); 42.26 (*t*); 45.72 (*t*); 49.76 (*q*); 69.32 (*s*); 124.60 (*d*); 141.48 (*d*); 144.83 (*d*); 150.99 (*s*); 161.40 (*s*).

To the soln. of the methiodide (0.43 g, 1.23 mmol) in anh. MeOH (35 ml) at 0°, $NaBH_4$ (0.06 g, 1.58 mmol) was added. The mixture was stirred at r.t. for 1 h, and then treated with ice. After evaporation, the residue was partitioned between H_2O and $CHCl_3$, the extract dried and evaporated, and the residue purified by FC ($CHCl_3$/MeOH 95:5): 0.14 g (50%) of **25**. ^{1}H-NMR ($CDCl_3$): 2.06–2.18 (*m*, 2 H); 2.20–2.32 (*m*, 2 H); 2.37 (*s*, MeN); 2.45–2.58 (*m*, 4 H); 3.02–3.10 (*m*, 1 CH_2N); 3.26 (*s*, 2 CH_2S). ^{13}C-NMR ($CDCl_3$): 27.36 (*t*); 33.83 (*t*); 41.13 (*t*); 45.97 (*q*); 46.85 (*t*); 52.06 (*t*); 52.27 (*t*); 75.98 (*s*); 135.13 (*s*); 137.15 (*s*). Anal. calc. for $C_{11}H_{17}NS_2$: C 58.10, H 7.54, N 6.16; found: C 57.96, H 7.48, N 5.98.

*1,2,3,4,5,6-Hexahydro-2-methyl-7*H*-cyclopenta[*c*]pyridin-7-one* (**2**). As described for **1**, from **25** (0.14 g) and $Tl(NO_3)_3 \cdot 3H_2O$ (0.9 g): **2** (67%). ^{1}H-NMR ($CDCl_3$): 2.36–2.66 (*m*, 8 H); 2.43 (*s*, MeN); 3.02–3.10 (*m*, 1 CH_2N).

On standing, tarry materials were formed from **2**. Thus, **2** was immediately transformed into the oxalate salt by reaction with 1 equiv. of oxalic acid in AcOEt. The oxalate salt of **2** was, however, too hygroscopic to determine the m.p. IR: 1700 (CO), 1660 (C=C). ^{1}H-NMR (D_2O): 2.38–2.46 (*m*, 2 H); 2.52–2.64 (*m*, 2 H); 2.68–2.84 (*m*, 2 H); 2.86 (*s*, MeN); 3.12–3.36 (*m*, 1 H, CH_2N); 3.46–3.68 (*m*, 2 H, CH_2N); 3.94 (*d*, *J* = 15.75, 1 H, CH_2N). ^{13}C-NMR (D_2O): 25.12 (*t*); 29.55 (*t*); 34.96 (*t*); 41.95 (*q*); 48.76 (*t*); 50.18 (*t*); 130.48 (*s*); 167.79 (*s*); 174.37 (*s*); 210.00 (*s*). MS: 151 (100, M^+), 150 (75), 123 (28), 122 (41), 108 (36), 94 (21), 79 (44). HR-MS: 151.09999 (calc. 151.09971).

*2,3,4,5,6,7-Hexahydro-7-oxo-1*H*-2,2-dimethylcyclopenta[*c*]pyridinium Iodide* (**26**). As described for **14**, from **2** (0.04 g): 0.03 g of **26**. M.p. 209–215° (dec.). ^{1}H-NMR (D_2O): 2.41–2.47 (*m*, 2 H); 2.57–2.67 (*m*, 2 H); 2.74–2.88 (*m*, 2 H); 3.02 (*s*, 2 MeN); 3.44–3.54 (*m*, 1 CH_2N); 3.94 (*s*, 1 CH_2N). ^{13}C-NMR (D_2O): 24.30 (*t*); 29.42 (*t*); 35.12 (*t*); 51.58 (*q*); 51.65 (*q*); 57.97 (*t*); 58.96 (*t*); 129.92 (*s*); 172.96 (*s*); 209.95 (*s*). Anal. calc. for $C_{10}H_{16}INO$: C 40.97, H 5.50, N 4.78; found: C 40.81, H 5.42, N 4.63.

Pharmacology. The new compounds were tested according to the already published protocol [9].

Molecular Modeling. Calculations were performed with the program PC Spartan Pro (version 1.01), *Wavefunction, Inc.*, 18401 Von Karman Ave., Suite 370, Irvine, CA 92612. The methods used were AM1 (semiempirical) and HF/6-31G* (*ab initio*). Compounds **1**, **2**, arecolone, and isoarecolone were calculated as the protonated form, since this is the form believed to interact with the receptor; the Me group was always equatorial and the H-atom axial. Superimpositions were performed by means of the program InsightII (MSI), with the O-atom, the N-atom, and axial N–H (or NMe group) as fitting points.

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