115. Synthesis and Conformation of (5*R*,8*R*,10*R*)-8-(Methylthiomethyl)ergoline-6-carboxamidine

by **René Nordmann*** and **Hans-Rudolf Loosli**

Pharmaceutical Division, Preclinical Research Department, *Sandoz Ltd.*, CH-4002 Basel

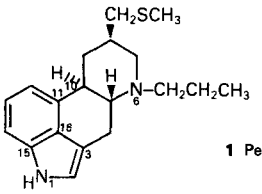
Dedicated to Prof. *Albert Eschenmoser* on the occasion of his 60th birthday

(15.III.85)

The title compound **7** and two related novel ergolines have been synthesised from (5*R*,8*R*,10*R*)-8-(methylthiomethyl)ergoline-6-carbonitrile (**4**). The guanidine function of **7** induces a boat conformation of ergoline-ring D, as demonstrated by a careful NMR spectroscopic analysis of **7** and its *N*-hydroxy congener **6**. Diphenylphosphinodithioic acid has been used to convert the cyanamide function of **4** into the thiourea function at (5*R*,8*R*,10*R*)-8-(methylthiomethyl)ergoline-6-thiocarboxamide (**5**).

Introduction. – In recent years a number of ergot derivatives have been described as dopamine agonists, and some of them have found use in the treatment of hyperprolactinemia, acromegaly and Parkinsonism. An impressive potentiation and prolongation of the dopaminomimetic action was obtained by introducing a propyl substituent into position 6 of the ergoline skeleton, as demonstrated first with pergolide (**1**) [1] and exemplified later with the N(6)-propyl analogues of lisuride and *trans*-dihydrolisuride [2].

In order to investigate further the influence of the N(6)-substituent on the dopaminomimetic activity, we decided to synthesize a derivative of pergolide (**1**), where N(6) would be part of a guanidine function. We report here the synthesis of (5*R*,8*R*,10*R*)-8-(methylthiomethyl)ergoline-6-carboxamidine **7**, together with its congeners **5** and **6**.

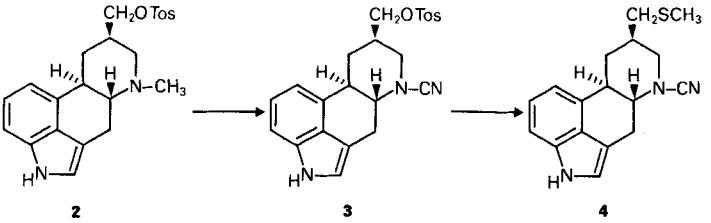


1 Pergolide

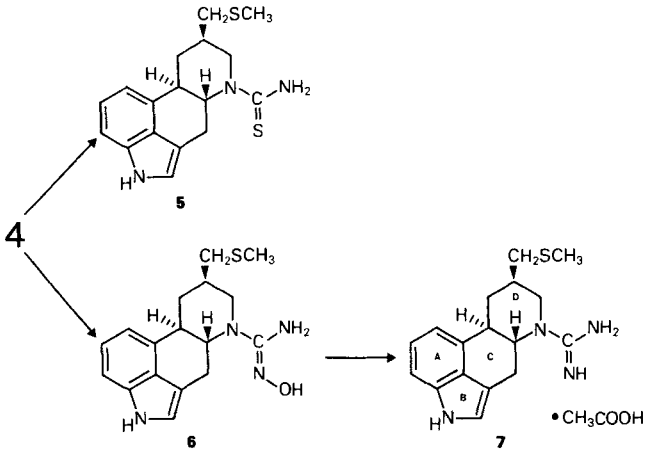
Chemistry. – The 6-ergolinecarbonitriles are well-known intermediates in the *von Braun* degradation of ergolines [3], and their partial hydrolysis to urea and isourea derivatives has been reported [4]. Therefore, **4** was chosen as intermediate for the synthesis of **7**: Tosylate **2** [5] was treated with cyanogen bromide in CH_2Cl_2 to yield a crystalline mixture of 6-ergolinecarbonitriles with **3** as major component *(Scheme 1)*[1]). Nucleophilic substitution with sodium methanethiolate in DMF afforded **4**. Thiourea **5** was obtained

[1]) The mass spectrum showed the presence of the 8-bromomethyl and 8-chloromethyl derivative as minor components.

Scheme 1



Scheme 2



from **4** after treatment with diphenylphosphinodithioic acid *(Scheme 2)*[2]) [6]. Addition of hydroxylamine to the cyanamide function of **4** resulted in *N*-hydroxyguanidine **6** which was reduced with Zn in AcOH/H_2O 1:1 to the desired guanidine **7**. Due to its high polarity, **7** was difficult to purify. Finally it was found, that after column chromatography on silica (CH_2Cl_2/CH_3OH/4N AcOH 80:20:2), the acetate salt **7** was prone to be precipitated from CH_3OH by addition of Et_2O.

(5*R*,8*R*,10*R*)-8-(Methylthiomethyl)ergoline-6-carboxamidine Acetate (7): Constitution, Configuration, and Conformation of Ring D. – Despite the trivial chemical conversion **6**→**7**, structural proof of **7** was not straightforward. In view of the unsatisfactory elemental analysis *(cf. Exper. Part)*, we had to rely on NMR-spectroscopic measurements. *Fig. 1* shows the ^{1}H-NMR spectrum of **6** (base) and **7** (acetate salt). Surprisingly, the pattern of the well separated signal of H_β–C(9) at high field clearly differs in the two spectra. In the spectrum of **6**, H_β–C(9) appears (as expected) as a *q* with 3 large *J*'s of 12 Hz (1 geminal and 2 vicinal), *cf. Fig. 2*. This pattern is characteristic for H_β–C(9) in 8β-substituted ergolines, ring D being in a chair conformation. But in the spectrum of **7**, the *J*'s of H_β–C(9), and on close examination also some other *J*'s ($J(8,9\alpha) = 6$, $J(8,9\beta) = 8$, $J(8,7\alpha) \leqslant 4$, and $J(8,7\beta) \leqslant 4$ Hz) clearly deviate from the usual values depicted in *Fig. 2*. This left us in some doubt about the proposed constitution and/or configuration of **7**. We embarked, therefore, on a careful NMR-spectroscopic analysis of **6**

[2]) Diphenylphosphinodithioic acid [6] has been used earlier to convert nitriles into thioamides [7].

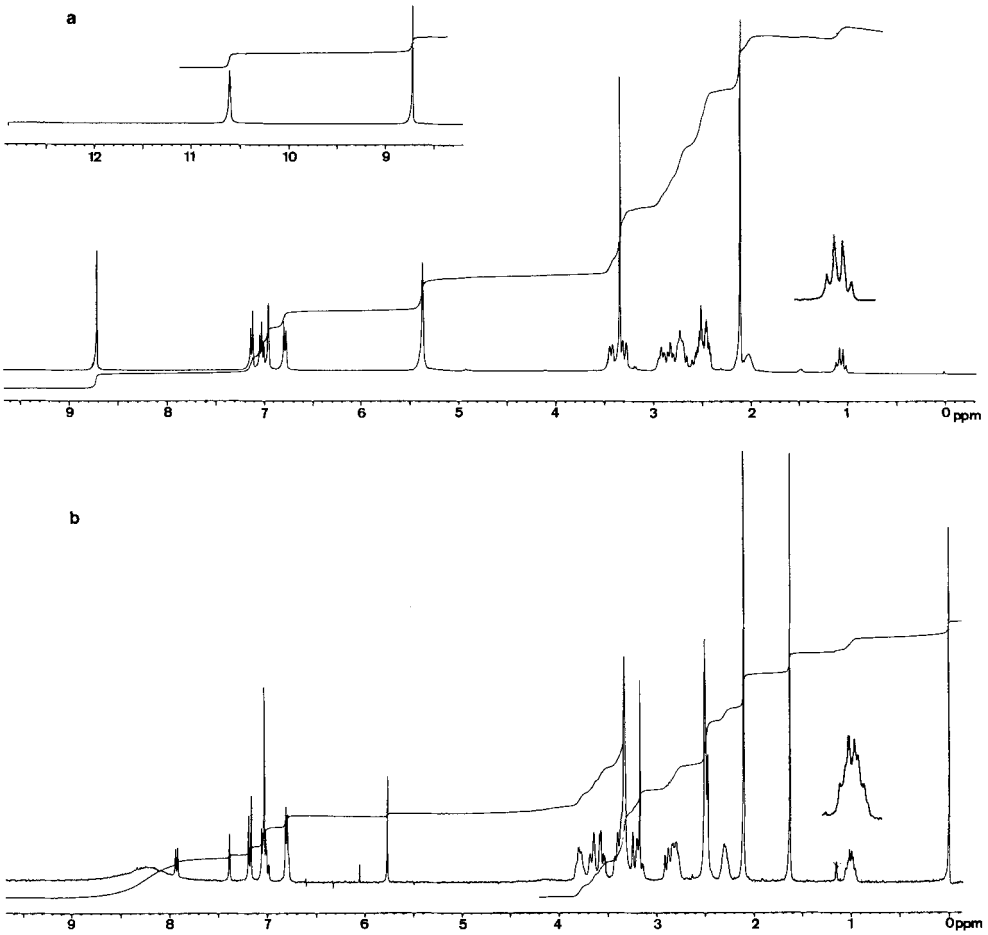


Fig. 1. *360-MHz-^{1}H-NMR spectra of* **6** *(*a*) and* **7** *(*b*) in DMSO.* Note the different patterns of H_β–*C(9)* at about 1 ppm (inset).

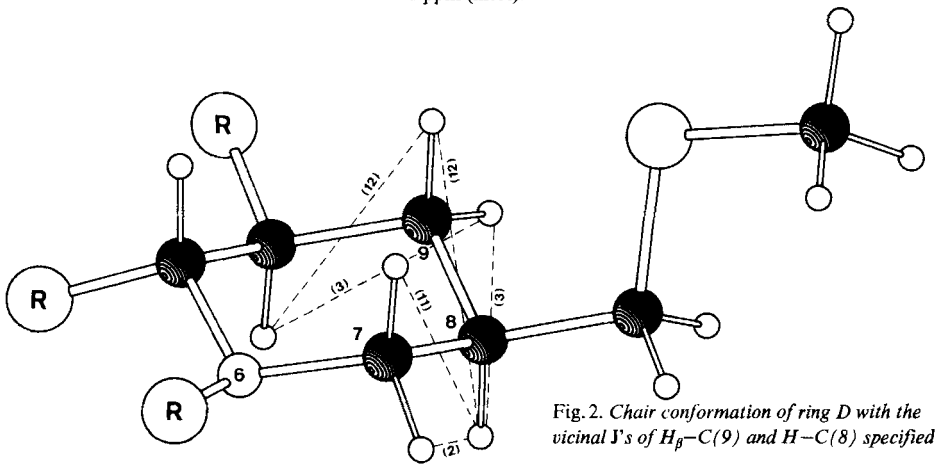


Fig. 2. *Chair conformation of ring D with the vicinal J's of H_β–C(9) and H–C(8) specified*

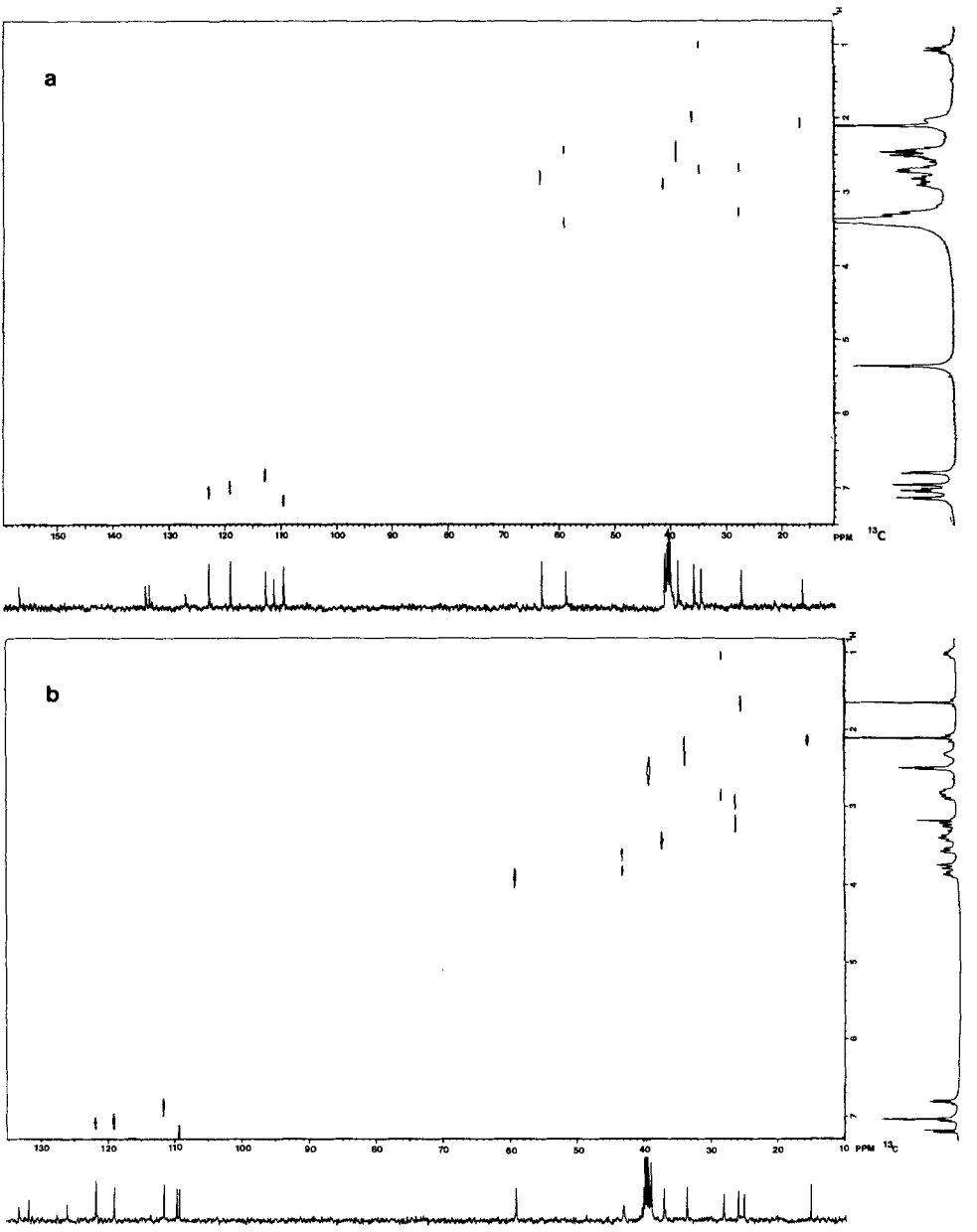


Fig. 3. *H,C-COSY-NMR spectra (two dimensional heteronuclear shift correlation) of* **6** *(*a*) and* **7** *(*b*) in DMSO*

and **7**, including double-resonance experiments in the ^{1}H-NMR spectra, ^{13}C-NMR-spectroscopic measurements and ^{1}H,^{13}C-2D-correlation-NMR spectroscopy [8] *(Fig. 3)*. As a result of this analysis, all signals of the ^{1}H- and ^{13}C-NMR spectra of **6** and **7** could be assigned, *cf. Table*. Constitution of **7** was now beyond any doubt, and we reexamined the unusual *J*'s in the ^{1}H-NMR spectrum of **7**, which had to be explained by a change of

Table. *Chemical Shifts (ppm, $\delta_{TMS} = 0$) of* **6** *and* **7** *in DMSO*

^1H			^{13}C		
Atom	**6**[a][b])	**7**[c])	Atom	**6**[a])	**7**[c])
H–N(1)	10.60	8.2	C(2)	119.00	119.05
H–C(2)	6.95	7.02	C(3)	111.23	109.76
H_α–C(4)	2.70	2.89	C(4)	27.30	25.86
H_β–C(4)	3.29	3.23	C(5)	63.19	59.15
H_β–C(5)	2.82	3.79	N(6)–*C*(=N)–NH_2	156.72	157.84
NH_2	5.38	8.2	C(7)	58.82	43.29
NH	–	8.2	C(8)	35.84	33.53
OH	8.71	–	CH_3SCH_2	38.71	38.81
H_α–C(7)	3.43	3.57[d])	CH_3SCH_2	16.29	14.93
H_β–C(7)	2.45	3.63[d])	C(9)	34.61	28.20
H_α–C(8)	2.03	2.28	C(10)	41.05	36.97
CH_3SCH_2	2.45–2.55	2.50	C(11)	134.12	131.78
CH_3SCH_2	2.11	2.11	C(12)	112.73	111.58
H_α–C(9)	2.72	2.81	C(13)	122.80	121.77
H_β–C(9)	1.08	1.02	C(14)	109.52	109.27
H_α–C(10)	2.92	3.40	C(15)	133.48	133.18
H–C(12)	6.80	6.80	C(16)	126.97	126.04
H–C(13)	7.03	7.02			
H–C(14)	7.13	7.18			

[a]) Base in DMSO.
[b]) Addition of 0.8 equiv. of AcOH does not induce shift differences ≥ 0.05 ppm.
[c]) Acetate salt in DMSO.
[d]) Signals could be interchanged.

configuration[3]) or conformation. Investigation of structural models led us to the assumption that ring D in **7** had adopted a boat conformation, resulting in a loss of the antiperiplanar relationship of axial vicinal protons, which would account for the observed change of the *J*'s. In order to investigate this assumption, we measured the NOE effects in the ^1H-NMR spectrum of **6** and **7**. The results of these measurements are shown in *Fig. 4*. Based on these, we conclude that ring D of **7** is indeed in a boat conformation. In addition, the NOE effect between H–C(8) and H–C(10) confirms the 8β-configuration in **7**.

Discussion. – The subtle difference between **6** and **7** is remarkable. Incorporation of N(6) into a guanidinium but not into a *N*-hydroxyguanidine function leads to a conformational change of ring D from chair to boat, presumably driven by an energetically favorable planarization of the guanidinium function. Investigation of structural models reveals that such a planarization ought to lead to a conformational change of ring D due to steric interference of a planar guanidinium with the equatorial proton H_β–C(4). Apparently, the planarization of the guanidinium function, allowing delocalization of the N(6)-electron lone pair, is energetically so favorable to overcome the necessary concomitant conformational change of ring D from chair to boat. Accordingly, we assume that the *N*-hydroxyguanidine function of **6** is not planar, which allows ring D to stay in its chair conformation.

[3]) The pattern of H_β–C(9) in the spectrum of **7** resembled somewhat that of an 8α-substituted ergoline (*td*); however, an epimerization at C(8) during the conversion **6**→**7** is chemically not reasonable.

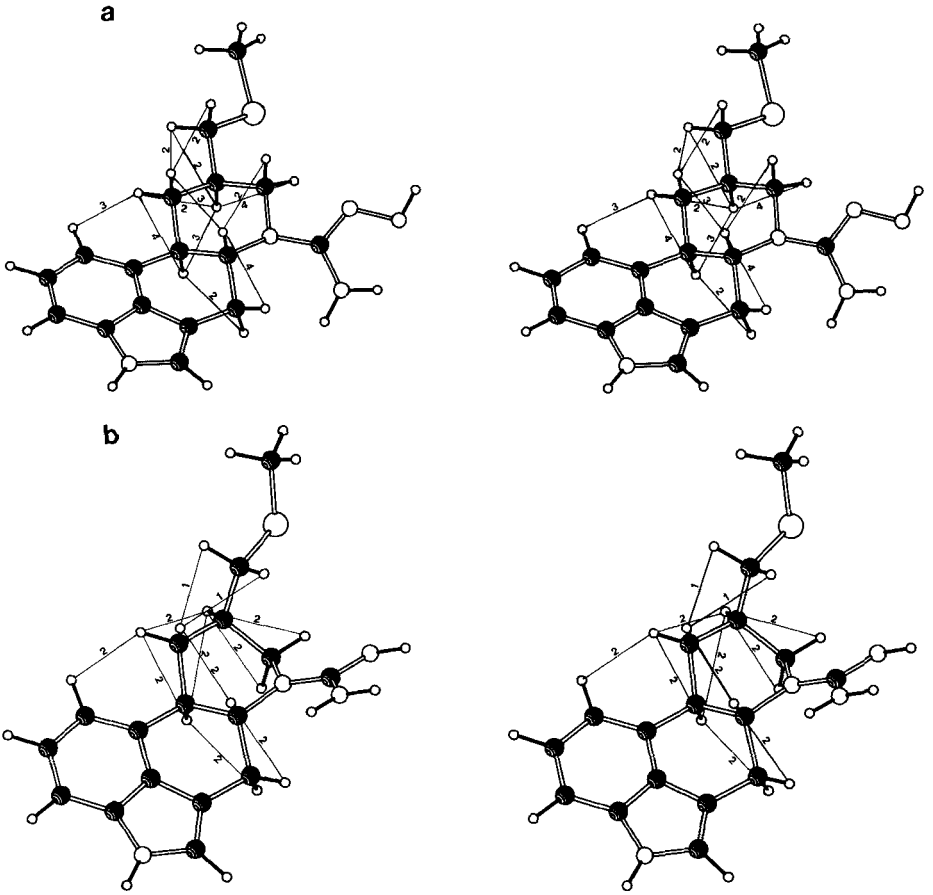


Fig. 4. *Stereoview of the major conformation of* **6** *(a) and* **7** *(b) in DMSO solution with some of the important homonuclear ^{1}H-NOE effects (thin lines).* The numbers are given in percent.

To our knowledge (5*R*,8*R*,10*R*)-8-(methylthiomethyl)ergoline-6-carboxamidine acetate (**7**) is the first ergoline reported with ring D in a boat conformation[4]).

Pharmacological Evaluation. – At doses of 1 mg/kg s.c., compounds **5**–**7** did not show any inhibition of basal prolactin release in male rats [10] 4 hours after application of the compounds (*cf.* pergolide (**1**): $ID_{50} = 1.3 \times 10^{-3}$ mg/kg s.c.). We conclude that the novel substituents on N(6) have completely abolished the dopamine agonistic activity of pergolide (**1**), most likely because of the change in, or delocalisation of, the basicity in this region of the molecule.

We thank *P. Graff* and *M. Kaiser* for their capable technical assistance in the synthetic work, *T. Zardin* for interpretation of NMR spectra and *U. Briner* for pharmacological testing.

[4]) A distorted chair conformation of ring D has been reported for methyl (5*R*,8*S*,10*S*)-6-methyl-10-methoxyergoline-8-carboxylate [9].

Experimental Part

General. M.p. were determined on a *Büchi-SMP-20* apparatus and are not corrected. IR ($\tilde{\nu}$ [cm^{-1}]): *Perkin Elmer 21.* $[\alpha]_D^{20}$: *Perkin Elmer 241 MC.* ^{1}H-NMR: *Bruker Spektrospin WH 360* (360 MHz) with TMS ($\delta = 0.00$ ppm) as internal standard. ^{13}C-NMR: *Bruker Spektrospin WH-360* (90.5 MHz). Mass spectra (MS): *CEC-21-110B* (FD), *AEI-MS-30* or *Varian-MAT-212* spectrometer (EI = electron ionisation, FD = field desorption; *m/z* (% relative abundance)).

(5R,8R,10R)-8-[(Tosyloxy)methyl]ergoline-6-carbonitrile (**3**). A mixture of tosylate **2** (67.2 g, 164 mmol) [5] and K_2CO_3 (13.8 g, 164 mmol) in CH_2Cl_2 (1.2 l) was treated with cyanogen bromide (37 g, 0.33 mol) and stirred at r.t. for 18 h. H_2O (250 ml) was added and stirring continued for 15 min. The org. layer was separated, extracted with 1N HCl, dried, and evaporated. The residue was redissolved in CH_2Cl_2 and precipitated by addition of hexane to yield 58.8 g (85%) of product with **3** as major component[1]). A sample was recrystallised from CH_2Cl_2/CH_3OH, m.p. 209–211°; $[\alpha]_D^{20} = +34°$ ($c = 0.5$, Py); IR (CH_2Cl_2, 5%): 3440*m*, 2420*s*, 1600*w*, 1440*m*, 1360*s*, 1185*s*, 1175*s*. ^{1}H-NMR ($CDCl_3$, 360 MHz): 1.18 (*q*, $J = 12$, H_β–C(9)); 2.3–2.4 (*m*, H–C(8)); 2.48 (*s*, 3H); 2.56 (br. *d*, $J = 12$, H_α–C(9)); 2.81 (*t*, $J = 12$, H_β–C(7)); 2.88–3.02 (*m*, H_α–C(4), H–C(5), H–C(10)); 3.34 (br. *d*, $J = 12$, H_β–C(4)); 3.59 (*md*, H_α–C(7)); 3.9–4.1 (*md*, 2H); 6.79 (*d*, $J = 8$, H–C(12)); 6.94 (*s*, H–C(2)); 7.17 (*t*, $J = 8$, H–C(13)); 7.24 (*d*, $J = 8$, H–C(14)); 7.40 (*d*, $J = 8$, 2H); 7.83 (*d*, $J = 8$, 2H); 8.10 (br. *s*, HN). MS (EI): 423 (12), 422 (34), 421 (100, M^+), 331 and 329 (9 and 7, resp. M^+; 8β-bromomethyl), 287 and 285 (21 and 70, resp. M^+; 8β-chloromethyl). Anal. calc. for $C_{23}H_{23}N_3O_3S$ (421.52): C 65.5, H 5.5, N 10.0, O 11.4, S 7.6; found: C 65.0, H 5.5, N 9.9, O 11.3, S 7.5.

(5R,8R,10R)-8-(Methylthiomethyl)ergoline-6-carbonitrile (**4**). A soln. of CH_3SH (28.4 ml) in DMF (200 ml) was treated at 0° in portions with NaH (16.8 g; 55% dispersion in oil, washed 3 times with hexane before use). To this suspension of CH_3SNa formed, a soln. of **3** (27 g, 64 mmol) in DMF (200 ml) was added dropwise. The mixture was stirred at 0° for 2 h and evaporated under high vacuum. The residue was partitioned between CH_2Cl_2 and H_2O and the org. layer dried and evaporated. The residue was crystallised from CH_2Cl_2/Et_2O to yield 13.7 g (74%) of **4**, uniform on TLC. A sample was recrystallised from CH_2Cl_2/CH_3OH, m.p. 178–180°; $[\alpha]_D^{20} = +59.7°$ ($c = 1.0$, 95% AcOH). IR (CH_2Cl_2, 5%): 3440*s*, 2220*s*, 1605*w*, 1440*m*, 1435*m*. ^{1}H-NMR ($CDCl_3$, 360 MHz): 1.18 (*q*, $J = 12$, H_β–C(9)); 2.15–2.25 (*m*), superimposed by 2.17 (*s*, together 4H); 2.4–2.6 (*md*, 2H); 2.77 (*t*, $J = 12$, H_β–C(7), partially superimposed by 2.82 (br. *d*, $J = 12$, H_α–C(9), together 2H); 2.9–3.05 (*m*, H_α–C(4), H–C(5), H–C(10)); 3.36 (br. *d*, $J = 12$, H_β–C(4)); 3.74–3.80 (*md*, H_α–C(7)); 6.91 (*d*, $J = 8$, H–C(12)); 6.94 (*s*, H–C(2), together 2H); 7.16 (*t*, $J = 8$, H–C(13)); 7.21 (*d*, $J = 8$, H–C(14), together 2H); 8.08 (br. *s*, HN). MS (EI): 299 (20), 298 (61), 297 (100, M^+), 270 (17), 250 (20), 236 (26). Anal. calc. for $C_{17}H_{19}N_3S$ (297.43): C 68.7, H 6.4, N 14.1, S 10.8; found: C 68.6, H 6.5, N 14.1, S 10.9.

(5R,8R,10R)-8-(Methylthiomethyl)ergoline-6-thiocarboxamide (**5**). A mixture of **4** (7.0 g, 23.6 mmol) and diphenylphosphinodithioic acid (11.8 g, 472 mmol) [6] in i-PrOH (400 ml) was stirred at 60°. After 10 min, the mixture was homogeneous, but 5 min later, a product started to precipitate. After 30 min, the mixture was evaporated and the residue partitioned between CH_2Cl_2 and 0.5N NaOH. The org. layer was separated and extracted with 1N $NaHCO_3$, dried, and evaporated. The residue was crystallised from CH_2Cl_2 to yield 4.5 g (58%) of **5**, m.p. 168–169° (dec.). A sample was filtered through a short silica column and recrystallised from CH_2Cl_2/Et_2O. $[\alpha]_D^{20} = -269,6°$ ($c = 0.98$, Py). IR (nujol): 3435*s*, 3380*s*, 3290*s*, 3200*s*, 1610*s*, 1500*s*. ^{1}H-NMR (DMSO, 360 MHz): 0.93 (*q*, $J = 12$, H_β–C(9)); 2.10 (*s*, 3H); 2.25–2.35 (*m*, H–C(8)); 2.45–2.7 (*m*(*d*), 2H); 2.7–2.8 (*m*, H_α–C(4), H_α–C(9)); 3.28 (*t*, $J = 12$, H–C(10)); 3.38–3.45 (*m*, H_β–C(4), H_β–C(7)); 3.75 (H_2O, H_2N); 4.17 (*td*, $J = 12$, 3, H–C(5)); 4.80 (*d*, $J = 12$, H_α–C(7)); 6.76 (*d*, $J = 8$, H–C(12)); 6.98 (br. *s*, H–C(2)); 7.04 (*t*, $J = 8$, H–C(13)); 7.18 (*d*, $J = 8$, H–C(14)); 8.15 (*d*, $J = 2$, HN). MS (EI): 333 (11), 332 (23), 331 (100, M^+), 284 (12), 272 (30). Anal. calc. for $C_{17}H_{21}N_3S_2$ (331.51): C 61.6, H 6.4, N 12.7, S 19.3; found: C 61.7, H 6.4, N 12.8, S 19.0.

(5R,8R,10R)-N²-Hydroxy-8-(methylthiomethyl)ergoline-6-carboxamidine (**6**). A mixture of **5** (5.3 g, 18 mmol), $NH_2OH \cdot HCl$ (5.0 g, 72 mmol), and Na_2CO_3 (11.5 g, 108 mmol) in DMF (180 ml) was stirred overnight at 80°. After cooling, the mixture was filtered and evaporated. The residue was suspended in CH_2Cl_2/H_2O and the insoluble fraction recovered by filtration. The filtercake was washed with cold CH_3OH and dried under high vacuum to yield 3.0 g (50%) of raw **6**. A sample was recrystallised from hot CH_3OH, m.p. 229–231°; $[\alpha]_D^{20} = -159°$ ($c = 1.0$, 95% AcOH). IR (nujol): 3450*s*, 3340*s*, 3290*s*, 3160*s*, 3060*m*, 1670*s*, 1620*w*, 1610*m*, 1600*m*. ^{1}H-NMR (DMSO, 360 MHz): see *Table* and *Fig. 1.* ^{13}C-NMR (DMSO, 90.5 MHz): see *Table.* MS (EI): 331 (20), 330 (75, M^+), 314 (29), 313 (100), 312 (20), 297 (13), 272 (32), 254 (78). Anal. calc. for $C_{17}H_{22}N_4OS$ (330.46): C 61.8, H 6.7, N 17.0, O 4.8, S 9.7; found: C 61.9, H 7.1, N 16.8, O 5.3, S 9.8.

(5R,8R,10R)-8-(Methylthiomethyl)ergoline-6-carboxamidine Acetate (**7**). A mixture of **6** (1.65 g, 5 mmol) and Zn powder (5 g) in $AcOH/H_2O$ 1:1 (30 ml) was stirred overnight at 50°. After filtration and evaporation,

another batch of Zn powder (5 g) was added and the mixture stirred again in AcOH/H_2O 1:1 (30 ml) at 50° for 3 days. The mixture was filtered and evaporated and the residue purified by medium-pressure liquid chromatography on silica (1.26 kg; CH_2Cl_2/CH_3OH/4N AcOH 80:20:2) to yield 1.23 g of raw **7**. This material was partitioned between BuOH and 2N K_2CO_3. The org. layer was separated, evaporated, and dried under high vacuum. The residue was dissolved in a small amount of CH_3OH and precipitated by slow addition of this soln. to Et_2O under stirring to afford 792 mg (42%) of acetate salt **7**, m.p. 155°; $[\alpha]_D^{20} = -143.1°$ (c = 1.0, 95% AcOH). IR (nujol): 3400–3000 (br.), 1655*s*, 1595*s*, 1560*s*. ^{1}H-NMR (DMSO, 360 MHz): see *Table* and *Fig. 1*. ^{13}C-NMR (DMSO, 90.5 MHz): see *Table*. MS (FD): 315 (100, MH$^+$), 314 (63, M^+). Anal. calc. for $C_{17}H_{22}N_4S \cdot C_2H_4O_2$ (374.51): C 60.9, H 7.0, N 15.0, O 8.5, S 8.6; found: C 57.3, H 6.7, N 13.9, O 9.6, S 7.8.

REFERENCES

[1] R.W. Fuller, J.A. Clemens, E.C. Kornfeld, H.D. Snoddy, E.B. Smalstig, N.J. Bach, *Life Sci.* **1979,** *24,* 375; D.L. Kleinberg, A. Lieberman, J. Todd, J. Greising, A. Neophytides, M. Kupersmith, *J. Clin. Endocrinol. Metab.* **1980,** *51,* 152.

[2] H. Wachtel, in 'Lisuride and other Dopamine Angonists', Eds. D.B. Calne, R. Horowski, R.J. McDonald, and W. Wuttke, Raven Press, New York, 1983, pp. 109–125.

[3] T. Fehr, P.A. Stadler, A. Hofmann, *Helv. Chim. Acta* **1970,** *53,* 2107.

[4] Y. Nakahara, T. Niwaguchi, *Chem. Pharm. Bull.* **1971,** *19,* 2337.

[5] E. Schreier, *Helv. Chim. Acta* **1958,** *41,* 1984.

[6] W.A. Higgins, P.W. Vogel, W.G. Craig, *J. Am. Chem. Soc.* **1955,** *77,* 1864.

[7] St.A. Benner, *Tetrahedron Lett.* **1981,** *22,* 1851.

[8] G.A Morris, L.D. Wall, *J. Am. Chem. Soc.* **1981,** *103,* 4703.

[9] L. Zetta, G. Gatti, *Tetrahedron* **1975,** *31,* 1405.

[10] E. Flückiger, U. Briner, W. Doepfner, E. Kovacs, P. Marbach, H.R. Wagner, *Experientia* **1978,** *34,* 1330.