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# ELECTROPHILIC SUBSTITUTION OF LITHIATED ERGOLINES

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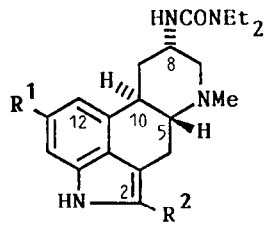
**SUMMARY:** Substitution of the ergoline derivative terguride **1** in the positions 2, 12 and 13 is effected by reaction of the respective bromo-ergolines with tert.-butyllithium and an electrophile in a regioselective manner.

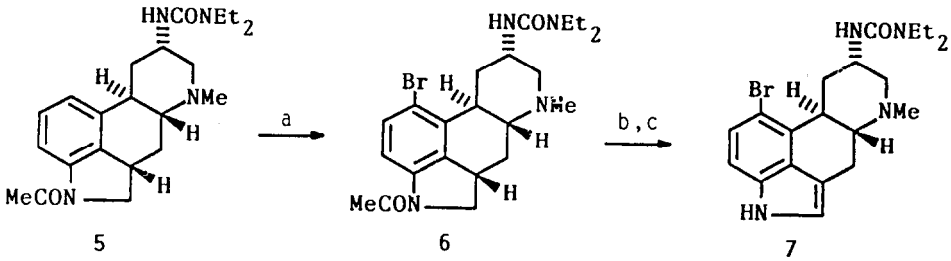
Bromination of the dopamine agonist lisuride (3-((5R,8S)-9,10-didehydro-6-methyl-8-ergolinyl)-1,1-diethyl-urea) provides 2-bromo-lisuride which is the first ergoline derivative with antidopaminergic properties.[1] This observation caused us to search for new possibilities of substitution of ergolines in position 2. The readily available 2-bromo derivative **2** prompted us to exchange bromine for lithium and to treat this intermediate with different electrophiles. This reaction sequence was also applied to ring A brominated ergolines for the introduction of otherwise unaccessible substituents.

Bromination[2,3] of the 1,1-diethyl-3-((5R,8S,10R)-6-methyl-8-ergolinyl)-urea[4] (terguride) with one equivalent of bromine gives the 2-bromo-ergoline **2** (dioxane, bromine, r.t., 15 min, 97%) with two equivalents in the presence of HBr the 2,13-dibromo compound **3** ($CH_2Cl_2$, two equivalents HBr in HOAc, bromine, yields **3**·HBr, 72%; $CH_2Cl_2$, KOH, 81%; total 58%). Selective debromination of **3** in position 2 can be effected by reduction with cobalt boride[5] (methanol, two equivalents $CoCl_2 \cdot 6\ H_2O$, $NaBH_4$ pellets, -40°C to 0°C, 2 h, from **3**·HBr 20%) or, preferably, with sodium hypophosphite in the presence of palladium on carbon[6] (HOAc, $NaH_2PO_2$, Pd/C 10%, 80°C, 16 h, from **3** 44%).




| | $R^1$ | $R^2$ |
|---|---|---|
| **1** | H | H |
| **2** | Br | H |
| **3** | Br | Br |
| **4** | H | Br |

The 2,3-dihydroergoline **5**, obtained by reduction[7] of **1** ($CF_3COOH$, $NaBH_4$ pellets,[8] -15°C, 2 h, 30%) and acetylation ($Ac_2O$, pyridine, r.t., 1 h, 80%) is selectively brominated in position 12. After hydrolysis of the acetyl group the 2,3-double bond is reintroduced by oxidation with tert.-butylhypochloride,[9] the total yield being 49%.

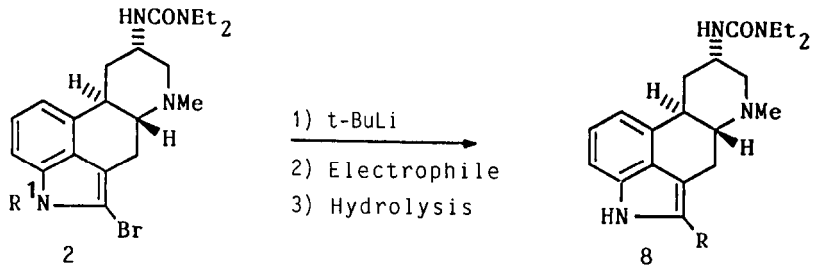



5 6 7

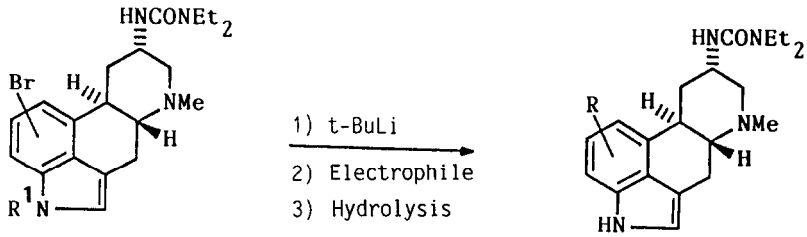
a: HOAc, NaOAc, 1 equiv. bromine within 1-2 min, r.t., 15 min (93%);
b: 1molar HCl, 70°C, 6 h (75%); c: THF, $NEt_3$, tert.-$C_4H_9OCl$, -40°C, 15 min, (70%).

Prior to halogen-metal exchange in position 2 the indole-NH has to be protected by silylation (LDA, TBDMSCl in THF). For bromine-lithium exchange in the positions 12 and 13 silylation facilitates the reaction but is not essential. Lithiation of the 1-TBDMS-bromo-ergolines is carried out with 10 equivalents of tert.-butyllithium[10] and tetramethylethylene diamine in toluene at -70°C within 5 min. The bromine-lithium exchange of the unprotected bromo-ergolines is performed in THF at -65°C by successive addition of 3 equivalents of methyl-lithium/lithium bromide solution[11] and, after 30 min, 10 equivalents of tert.-butyllithium followed by 30 min of stirring

In each case 10 equivalents of an electrophile are added and stirring is continued at the metalation temperature. After 30 to 60 min the temperature is slowly raised to room temperature, the TBDMS group is cleaved as indicated in the table and the products are isolated and purified by chromatography.




2 8




**4** (13-Br)
**7** (12-Br)

**9** (13-R)
**10** (12-R)

Table: Reaction of Lithio-Ergolines with Electrophiles

| Substrate R[1] | | Electrophile | a) | Product[15] | R | Yield [%] | mp. [°C] | $[\alpha]_D^{25}$ (conc. solvent[b]) |
|---|---|---|---|---|---|---|---|---|
| **2** | TBDMS | $(CH_3)_3SiN{=}C{=}O$ | A | **8a** | 2-$CONH_2$ | 88 | 171-173 | +42° (0.5 py) |
| **4** | TBDMS | $(CH_3)_3SiN{=}C{=}O$ | B | **9a** | 13-$CONH_2$ | 60 | 190 (dec.) | +11° (0.5 c) |
| **2** | TBDMS | $CO_2$ | - | **8b** | 2-COOH[12] | 48 | 260 (dec.) | +26° (0.2 m) |
| **4** | TBDMS | $CO(OCH_3)_2$ | B | **9c** | 13-$COOCH_3$ | 11 | 226-230 (dec.) | -9° (0.5 c) |
| **7** | H | $CO(OCH_3)_2$ | - | **10c** | 12-$COOCH_3$ | 46 | 95-103 (dec.) | +75° (0.5 c) |
| **4** | TBDMS | DMF[13] | B | **9d** | 13-CHO | 50 | 119-122 | -11° (0.5 c) |
| **7** | H | DMF | - | **10d** | 12-CHO | 53 | 154-159 (dec.) | +21° (0.5 c) |
| **4** | TBDMS | $C_6H_5NO_2$[14] | C | **9e** | 13-OH | 23 | 188-195 (dec.) | +11° (0.5 m) |
| **7** | H | $B(OCH_3)_3$,HOAc,$H_2O_2$ | - | **10e** | 12-OH | 47 | 145 (dec.) | +18° (0.5 c) |

a) cleavage of TBDMS group: method A: methanol and silica gel, r.t.; method B: methanol, 7molar KOH, r.t.; method C: $CF_3COOH$ with 1% water, 50°C.

b) py = pyridine, c = chloroform, m = methanol

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## REFERENCES AND NOTES

This work is dedicated to Prof. Dr. Rudolf Wiechert on the occasion of his 60th birthday.

1. H. Wachtel, W. Kehr, and G. Sauer, Life Science, 33, 2583 (1983).
2. F. Troxler and A. Hofmann, Helv. Chim. Acta, 40, 2160 (1957).
3. T. Fehr and H. Hauth, German Patent, No. 2347325 (1973).
4. G. Sauer, G. Haffer, and H. Wachtel, Synthesis, 1986, 1007.
5. L. Bernardi, G. Bosisio, C. Elli, B. Patelli, A. Temperilli, G. Arcari, and H.A. Glaesser, Il Farmaco, Ed. Sci., 30, 789 (1975).
6. S.K. Boyer, J. Bach, J. McKenna, and E. Jagdmann, J. Org. Chem., 50, 3408 (1985).
7. P. Gull and H. Hauth, German Patent No. 2810774 (1977).

8. The use of $NaBH_4$ in pellet form is highly recommended, powdered $NaBH_4$ might cause a violent explosion of hydrogen which is formed vigorously during addition to trifluoroacetic acid.
9. M. Kawase, Y. Miyake, and Y. Kikugawa, J. Chem. Soc. Perkin Trans. I, 1984, 1401.
10. D. Seebach and H. Neumann, Chem. Ber., 107, 847 (1974).
11. J.T. Sharp and C.E.D. Skinner, Tetrahedron Lett., 1986, 869.
12. Esterification in methanol/HCl at r.t., m.p. 175°C (dec.), $[\alpha]_D$: +33° (0.1 py) (as hydrogentartrate).
13. DMF protonates 2-lithio-ergoline.
14. G. Köbrich and P. Buck, Chem. Ber., 103, 1412 (1970).
15. **2**: m.p. 168-173°C; $[\alpha]_D$: +17° (c 0.5); $^1$H-NMR ($CDCl_3$) δ: 1.60 (1H, td, J=12, J=4 Hz, 9ß-H), 2.18 (1H, td, J=10, J=5 Hz, 5ß-H), 2.45 (3H, s, N-$CH_3$), 2.48 (1H, dd, J=11, J=3 Hz, 7ß-H), 2.53 (1H, dd, J=19, J=11 Hz, 4α-H), 2.78 (1H, dm, J=12 Hz, 9α-H), 2.87 (1H, dt, J=11, J=2 Hz, 7α-H), 2.98 (1H, ddd, J=12, J=10, J=4 Hz, 10α-H), 3.22 (1H, dd, J=15, J=5 Hz, 4ß-H), 4.27 (1H, m, 8-H), 5.50 (1H, d, J=7 Hz, NH), 6.87 (1H, m, 14-H), 7.11 (2H, m, 12-H, 13-H), 8.17 (1H, s, 1-NH). **3**: m.p. 208-213°C (dec.); $[\alpha]_D$: +1° (m 0.1). **4**: m.p. 213-218°C (dec.); $[\alpha]_D$: -8° (m 0.5); $^1$H-NMR (py-$d_5$) δ: 1.57 (1H, td, J=12, J=4 Hz, 9ß-H), 2.09 (1H, td, J=10, J=5 Hz, 5ß-H), 2.28 (3H, s, N-$CH_3$), 2.34 (1H, dd, J=11, J=2 Hz, 7ß-H), 2.67 (1H, ddd, J=15, J=11, J=1 Hz, 4α-H), 2.88 (1H, dt, J=11, J=2 Hz, 7α-H), 2.99 (1H, dm, J=12 Hz, 9α-H), 3.2-3.4 (2H, m, 4ß-H, 10α-H), 4.53 (1H, m, 8-H), 5.82 (1H, d, J=7 Hz, NH), 7.13 (1H, s, 12-H), 7.19 (1H, s, 2-H), 7.63 (1H, s, 14-H), 11.90 (1H, s, 1-HN). **5**: m.p. 130-133°C (dec.); $[\alpha]_D$: +30° (c 0.5). **6**: m.p. 120-127°C; $[\alpha]_D$: +31° (c 0.5). **7**: m.p. 163-180°C (dec.); $[\alpha]_D$: -0.3° (c 0.5); $^1$H-NMR ($CDCl_3$) δ: 1.51 (1H, td, J=12, J=4 Hz, 9ß-H), 2.28 (1H, td, J=10, J=9 Hz, 5ß-H), 2.42 (3H, s, N-$CH_3$), 2.88 (1H, dt, J=11, J=2 Hz, 7α-H), 3.98 (1H, dq, J=12, J=2 Hz, 9α-H), 4.28 (1H, m, 8-H), 5.43 (1H, d, J=8 Hz, NH), 6.88 (1H, t, J=1 Hz, 2-H), 7.03 (1H, d, J=8 Hz, 14-H), 7.27 (1H, d, J=8 Hz, 13-H), 8.08 (1H, s, 1-HN). **8a**: $^1$H-NMR ($CDCl_3$) δ: 1.54 (1H, td, J=12, J=3 Hz, 9ß-H), 2.40 (3H, s, N-$CH_3$), 6.73 (1H, d, J=8 Hz, 12-H), 7.05-7.15 (2H, m, 13-H, 14-H), 9.20 (1H, m, 1-HN). **9c**: $^1$H-NMR ($CD_3OD$) δ: 1.62 (1H, td, J=12, J=4 Hz, 9ß-H), 2.18 (1H, td, J=10, J=5 Hz, 5ß-H), 2.58 (1H, dd, J=12, J=3 Hz, 7ß-H), 2.67 (1H, ddd, J=15, J=10, J=1 Hz, 4α-H), 2.78 (1H, dq, J=12, J=2 Hz, 9α-H), 2.95-3.01 (2H, m, 7α-H, 10α-H), 3.48 (1H, dd, J=15, J=5 Hz, 4ß-H), 4.20 (1H, m, 8-H), 7.15 (1H, d, J=1 Hz, 2-H), 7.48 (1H, s, 12-H), 7.93 (1H, s, 14-H). **10d**: $^1$H-NMR ($CDCl_3$) δ: 2.45 (3H, s, N-$CH_3$), 6.98 (1H, s, 2-H), 7.25 (1H, d, J=8 Hz, 14-H), 7.69 (1H, d, J=8 Hz, 13-H), 10.27 (1H, s, 12-CHO).

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