HETEROCYCLES, Vol. 68, No. 5, 2006, pp. 879 - 884. © The Japan Institute of Heterocyclic Chemistry
Received, 30th January, 2006, Accepted, 28th March, 2006, Published online, 28th March, 2006. COM-06-10681

SYNTHESIS AND REACTIVITY OF DIBENZ[*d,g*]AZECIN-14(5*H*)-ONES

Patrick Mohr, Jochen Lehmann, and Michael Decker*

Department of Pharmaceutical/Medicinal Chemistry, Institute of Pharmacy, Friedrich-Schiller-University Jena, Philosophenweg 14, D-07743 Jena, Germany
m.decker@uni-jena.de

Abstract – Ring cleavage of the central *C,N*-bond in quaternary dibenz[*a,h*]quinolizinium salts with sodium hydride in DMSO yielded novel dibenz[*d,g*]azecin-14(5*H*)-ones, which produce cyclic carbinolamine derivatives in an acidified medium by transannular interaction. Investigations into the optimization of the NaH/DMSO reaction as ring cleaving reaction were performed. The ketone moiety of the azecinones is remarkably stable towards different reductive agents most probably due to steric hindrance, because also the quaternary ammonium salts which are unable to recyclize to carbinolammonium salts could not be reduced either. The compounds were screened for their affinity to hD_1-, hD_2- and hD_3-receptor subtypes, but did not show significant affinity in strong contrast to analogues without the ketone moiety.

Based on the lead structure **LE 300** (7-methyl-6,7,8,9,14,15-hexahydro-5*H*-indolo[3,2-*f*][3]benzazecine (**1**), which shows nanomolar affinities at the hD-receptor subtypes,[1,2,3] and the highly potent dopamine receptor ligand **LE 404** (7-methyl-5,6,7,8,9,14-hexahydrodibenzo[*d,g*]azecin-3-ol) (**2**) with subnanomolar affinity for the hD_1-receptor and nanomolar affinities for the hD_{2L}-, hD_3-, hD_4- and hD_5-receptor subtype,[4] we synthesized different substituted dibenz[*d,g*]azecines.[5] High-affinity chlorinated compounds loose their chlorine-atoms under Birch conditions, which were applied in the last step of the synthesis to yield the respective dibenz[*d,g*]azecines out of chlorinated dibenzoquinolizines.[5] Out of this reason we were looking for alternative cleaving methods for quinolizinium salt (Scheme 1).

Kulkarni *et al.* have described reductive cleavage of the central *C,N*-bond of the quaternary salt alkaloid stylopine using sodium hydride and dimethyl sulfoxide (NaH/DMSO) thus producing a tetrahydrobenz-

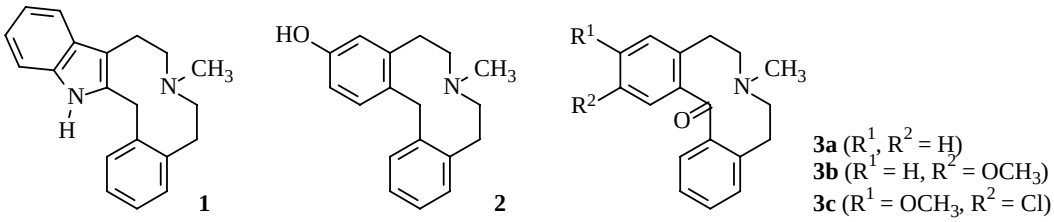
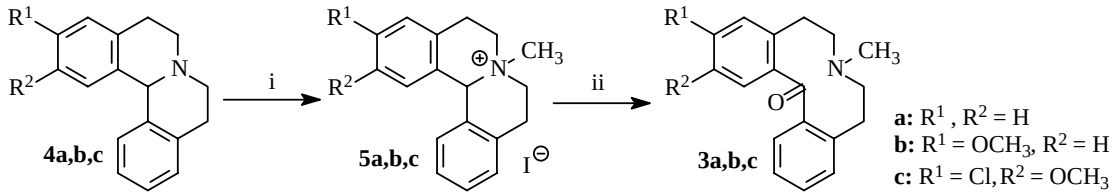


Figure 1. Lead structures LE 300 (**1**) and LE 404 (**2**); dibenz[*d,g*]azecin-14(5*H*)-ones (**3a-c**)

[*c,g*]azecine derivative, which could be subsequently oxidized (*m*-CPBA) to the corresponding benzazecinone protopine.[6] This method appeared promising, therefore we applied it for cleaving the central *C,N*-bond in quinolizinium salts (**5a-c**), which can be obtained by methylation of 5,8,9,13b-tetrahydro-6*H*-isoquino[1,2-*a*]isoquinolines (**4a-c**), the synthesis of which was described previously (Scheme 1).[4,5]



Scheme 1.Reagents and conditions: (i) MeI, 20 h, rt, 84 % (**5a**) / 61 % (**5b**), 91% (**5c**); (ii) NaH/DMSO, 68 % (**3a**) / 60 % (**3b**), 36% (**3c**)

Surprisingly, we directly obtained 7-methyl-6,7,8,9-tetrahydrodibenz[*d,g*]azecin-14(*5H*)-ones (**3a,b,c**) by treatment of **5a,b,c** with sodium hydride in DMSO without an additional oxidation step.[7,8]

To further elucidate the conditions for the reaction of quinozilinium salts with sodium hydride in DMSO and the formation of dibenz[*d,g*]azecinones, we applied various conditions for this reaction step and analyzed yields and reaction products. The best results in terms of yield are obtained by adding portionwise small amounts of sodium hydride over several hours to a solution of the respective quaternary salt (**5a,b,c**) in DMSO at room temperature. Either using excess quantities of sodium hydride or adding a warm suspension of sodium hydride in DMSO to the salt solution in one step leads to the formation of by-products and therefore poor yields. Conditions applying a warm suspension lead almost solely to by-products. In the case of substituted 7-methyl-5,8,9,13b-tetrahydro-6*H*-isoquino[1,2-*a*]isoquinolinium salts (**5b,c**) two by-products were formed. These findings in addition to isolation and spectroscopic analysis of these products showed that ring-cleavage of one of the six-membered rings occurs to form a double bond (Hofmann product). The formation of Hofmann products has been previously described in the literature for berberine-type alkaloids.[6,9] The reaction also takes place under nitrogen, therefore any oxidation by air oxygen can be ruled out, which proves that DMSO is the oxygen donating reagent. Therefore this reaction seems to be closely related to the mechanism of the Kornblum oxidation, i.e. the formation of carbonyl groups out of halides by the use of DMSO and base. According to a mechanism

proposed by Torsell, the reaction includes the formation of alkoxydimethylsulfonium ions, which yield in a carbonyl compound and dimethyl sulfide in the presence of a base as a concerted reaction.[10]

An interesting behaviour of the dibenz[*d,g*]azecin-14(5*H*)-ones (**3a-c**) can be observed after acidification. Transannular interaction takes place in this 10-membered ring system forming carbinolammonium salts (Figure 2) (**6a-c**).[7,8] The carbinolammonium salts (**6a-c**) do not show any carbonyl absorption in their IR spectra, which is very prominent for the bases (e.g. $\nu/c = 1644$ cm^{-1} for **3a**) and in addition the ^{13}C-NMR of **3b** showed a signal of the carbonyl group at 191.6 ppm, whereas after addition of CF_3COOD this signal disappeared and a new signal at 94.7 ppm to be assigned to the carbinolamine carbon can be observed.[8]

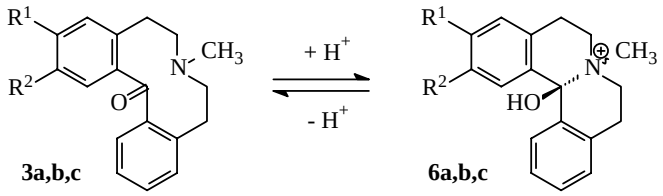


Figure 2. Transannular interaction of compounds (**3a-c**) in acidic medium to carbinolamines (**6a-c**).

These observations are in accordance with previous findings for cyclic aminoketones,[11] and for the alkaloids protopine and cryptopine, which are dibenz [*c, g*]azecinone derivatives.[12]

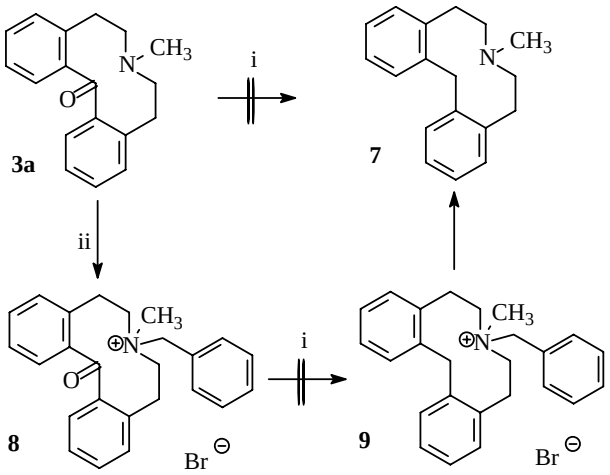
An appropriate reduction method for the carbonyl group should lead to potent dopamine receptor antagonists with 7-methyl-5,6,7,8,9,14-hexahydrodibenzo[*d,g*]azecine structure (like compound (**2**)). We have applied a couple of methods to reduce the carbonyl moiety in **3a-c** in order to avoid Birch conditions leading to removal of chlorine-atoms[5] and get an alternative route to chlorinated derivatives of **2**.

Due to the formation of carbinolammonium salts (**6**) in acidic medium, alkaline reduction conditions (pyridine) were selected.[13] The use of lithium aluminium hydride/pyridine, lithium aluminium hydride/aluminium chloride, sodium borohydride/aluminium chloride, and hydrogen/Adams catalyst, respectively, turned out to be unsuccessful. In each case starting material was recovered (Scheme 2).

Both the formation of carbinolammonium salts (**6**) and the extraordinarily low reactivity of the ketone moiety in the dibenz[*d,g*]azecin-14(5*H*)-ones (**3**) can be attributed to an intramolecular Bürgi-Dunitz trajectory, i. e. a favoured bonding alignment of a nucleophile (in this case the nitrogen atom) with the empty π^*-orbital of the ketone group,[14] especially since in a medium-sized azecine ring these two groups can easily interact. For the symmetric compound (**3a**) the carbonyl *C*-atom cannot be observed in the ^{13}C-NMR spectrum, probably because the time scales at room temperature for interaction and the one for the NMR-experiment do not differ significantly. To our knowledge such a stability of a carbonyl group towards strong reducing agents even under alkaline conditions has not yet been described.

In order to definitely exclude the formation of a carbinolamine derivative, compound (**3a**) was quaternized using benzyl bromide (Scheme 2). ^{13}C-NMR and IR spectra of compound (**8**) clearly show

the presence of a carbonyl group (δ = 204 ppm, ν/c = 1669 cm^{-1}), indicating that benzylation did take place at the nitrogen atom and not at the carbinolamine-oxygen atom. Intramolecular Bürgi-Dunitz trajectory is not possible anymore, so that the ketone form (**3a**) is stabilized. Much to our surprise, also compound (**8**) could not be reduced under the above mentioned reduction conditions. Therefore we conclude that steric hindrance around the carbonyl function in these 10-membered cyclic aminoketones is responsible for this remarkable stability.



Scheme 2.Reagents and conditions: (i) $LiAlH_4$-$AlCl_3$, $NaBH_4$-$AlCl_3$, $LiAlH_4$-pyridine, or H_2-PtO_2, respectively; (ii) benzyl bromide, 24 h, 70 °C, 60 %.

The dibenz[*d,g*]azecin-14(5*H*)-ones (**3a-c**) were tested for their affinity towards the human dopamine receptors hD_1, hD_{2L} and hD_3.[15] None of the compounds synthesized showed any significant affinity to one of the dopamine receptors tested. This is an interesting fact concerning SAR, because it is in a remarkable contrast to the dibenzo[*d,g*]azecines which are highly potent antagonists.[4,5] The two aromatic rings and the basic nitrogen which are essential for strong affinity to these receptors are obviously shifted by the planar carbonyl function into conformational positions which are not tolerated by the dopamine binding sites. In addition, the conformation of the azecinones is highly rigid, whereas the azecines are only moderately rigid and therefore can fit much better into the receptor.

In conclusion, we have synthesized dibenz[*d,g*]azecin-14(5*H*)-ones (**3a-c**) out of quaternary quinolizinium salts by reaction with sodium hydride in DMSO. The azecinones obtained form carbinolammonium salts in acidic medium by transannular interaction. The carbonyl group of the azecinones is extremely stable even towards highly reactive reductive agents.

ACKNOWLEDGEMENTS

Financial support for M. Decker by the ´Fonds der Chemischen Industrie´ (FCI) is gratefully acknowledged.

REFERENCES AND NOTES

1. T. Witt, F. J. Hock, and J. Lehmann, *J. Med. Chem.*, 2000, **43**, 2079.
2. M. Decker, K-.J. Schleifer, M. Nieger, and J. Lehmann, *Eur. J. Med. Chem.*, 2004, **39**, 481.
3. M. Decker and J. Lehmann, *Pharmazie*, 2006, **3**, 248.
4. B. Höfgen, M. Decker, P. Mohr, A. M. Schramm, S. A. F. Rostom, H. El-Subbagh, P. M. Schweikert, D. R. Rudolf, M. U. Kassack, and J. Lehmann, *J. Med. Chem.*, 2006, **49**, 760.
5. P. Mohr, M. Decker, C. Enzensperger, and J. Lehmann, *J. Med. Chem.*, 2006, **49**, 2110.
6. B. K. Kulkarni, R. K. Dhar, and N. J. de Souza, *J. Heterocycl. Chem.*, 1990, **27**, 623.
7. *7-Methyl-6,7,8,9-tetrahydrodibenz[d,g]azecin-14(5H)-one* (**3a**). To a solution of 0.11 g (0.29 mmol) of **5a** in 3 mL of DMSO were added little pieces of sodium hydride (overall 24 mg) over 7 h. The suspension was poured into 30 mL of water and extracted three times with 30 mL of ether. The combined organic phases were removed under reduced pressure and the residue crystallized with ether to yield white crystals (53 mg, 68 %). ^{1}H-NMR (250 MHz, $CDCl_3$): 1.91 (s, 3H, N-C$\underline{H}_3$), 2.20-2.9 (m, 8H, Ph-C$\underline{H}_2$-C$\underline{H}_2$), 7.15-7.20 (d, 6H, arom.), 7.28-7.35 (m, 2H, *J* = 7.5 Hz, arom.); ^{13}C-NMR ($CDCl_3$): 31.95 (2x Ph-$\underline{C}H_2$), 41.92 (N-$\underline{C}H_3$), 59.31 (2x Ph-CH_2-$\underline{C}H_2$), 125.98 (C1, C13), 128.04 (C2, C12), 129.88 (C4, C10), 130.16 (C3, C11), 139.77 (C4a, C9a), 141.63 (C13a, C14a); IR (KBr, cm^{-1}): 3414, 2927, 2357, 1644, 1258, 757, 666; MS (EI): m/z (% rel. Int.) = 265 (M^+, 58), 250(7), 236(16), 221(79), 205(11), 193(28), 179(100), 165(32), 146(56), 133(22), 115(14), 103(16), 91(18), 77(20), 71(70), 58(23), 51(7).

   13b-Hydroxy-7-methyl-5,8,9,13b-tetrahydro-6H-isoquino[1,2-a]isoquinolinium chloride (**6a**): mp 227 °C; ^{1}H-NMR (250 MHz, MeOD): 2.39 (s, 3H, N-C$\underline{H}_3$), 2.65-2.68 (m, 4H, Ph-C$\underline{H}_2$), 3.17-3.67 (m, 4H, Ph-CH_2-C$\underline{H}_2$), 6.67-6.83 (m, 8H, arom.); ^{13}C-NMR (MeOD): 24.63 (2x Ph-$\underline{C}H_2$), 45.53 (N-$\underline{C}H_3$), 54.52 (2x Ph-CH_2-$\underline{C}H_2$), 95.74 (C-OH), 128.35 (C1, C13), 129.94 (C2, C12), 130.42 (C3, C11), 131.05 (C4, C10), 131.62 (C13a, C14a), 134.71 (C4a, C9a); IR (KBr, cm^{-1}): 3414, 2717, 2357, 1429, 1207, 760; Anal. Calcd for $C_{18}H_{20}NOCl \times {}^{1}/_{8}\ H_2O$: C, 71.1; H, 6.7; N, 4.6. Found: C, 71.1; H, 6.9; N, 4.5.
8. Compounds (**3b** and **3c**) were prepared according to footnote 7.

   a) *3-Methoxy-7-methyl-6,7,8,9-tetrahydrodibenz[d,g]azecin-14(5H)-one* (**3b**). White crystals, mp 116 °C; ^{13}C-NMR ($CDCl_3$): 32.02 (Ph-$\underline{C}H_2$), 33.20 (Ph-$\underline{C}H_2$), 41.95 (N-$\underline{C}H_3$), 55.24 (O-$\underline{C}H_3$), 59.49 (Ph-CH_2-$\underline{C}H_2$), 59.86 (Ph-CH_2-$\underline{C}H_2$), 110.58 (C2), 115.51 (C4), 125.87 (arom.), 127.62 (arom.), 129.94 (arom.), 129.94 (arom.), 130.28 (arom.), 134.93 (C13c), 140.25 (C9a), 142.29 (C4a), 142.62 (C13a), 160.97 (C3), 191.61 (Ph-$\underline{C}$-Ph) ppm; IR (KBr, cm^{-1}): 3447, 2945, 2842, 1638, 1600, 1490, 1445, 1245; MS (EI): m/z (% rel. Int.) = 295 (M^+, 47.2), 280(7.1), 266(7.5), 251(66.5), 237(8.5), 223(17.1), 209(42.5), 193(15.7), 176(40.6), 165(29.6), 146(29.5), 133(11.9), 115(10.7), 103(10.6),

91(17.0), 71(100.0), 58(30.0); HRMS Calcd for $C_{19}H_{21}NO_2$: 296.1646. Found 296.1650.

13b-Hydroxy-3-methoxy-7-methyl-5,8,9,13b-tetrahydro-6H-isoquino[1,2-a]isoquinolinium chloride (**6b**): White crystals, mp 235 °C; ^{1}H-NMR (250 MHz, $CF_3COOD/CDCl_3$): 2.97 (s, 3H, N-C$\underline{H}_3$), 3.01-3.31 (mc, 4H, Ph-C$\underline{H}_2$), 3.61-3.82 (mc, s, 5H, Ph-CH$_2$-C$\underline{H}_2$, O-C$\underline{H}_3$), 3.82-4.08 (m, 2H, Ph-CH$_2$-C$\underline{H}_2$), 6.62-6.69 (dd, *J* = 2.5 Hz, 1H, arom., H4), 6.71-6.82 (dd, *J* = 2.5, 8.8 Hz, 1H, arom., H2), 7.11-7.19 (dd, 1H, arom., H10), 7.19-7.38 (mc, 3H, arom., H11-13), 7.38-7.50 (d, 1H, arom., H1) ppm; ^{13}C-NMR ($CF_3COOD/CDCl_3$): 23.52 (Ph-$\underline{C}H_2$), 23.73 (Ph-$\underline{C}H_2$), 45.19 (N-$\underline{C}H_3$), 53.69 (Ph-CH$_2$-$\underline{C}H_2$), 53.89 (Ph-CH$_2$-$\underline{C}H_2$), 55.41 (O-$\underline{C}H_3$), 94.66 (C-OH), 113.51 (C2), 114.11 (C4), 124.46 (C13c), 127.80 (arom.), 128.86 (arom.), 128.88 (arom.), 129.09 (arom.), 130.41 (arom.), 130.56 (arom.), 130.57 (arom.), 132.40 (C4a), 160.68 (arom., C3) ppm.

b) *3-Chloro-2-methoxy-7-methyl-6,7,8,9-tetrahydrodibenz[d,g]azecin-14(5H)-one/3-chloro-13b-hydroxy-2-methoxy-7-methyl-5,8,9,13b-tetrahydro-6H-isoquino[1,2-a]isoquinolinium chloride* (**3c**/**6c**); White crystals, mp 170 °C (**3c**); ^{1}H-NMR (**6c**, 250 MHz, MeOD): 3.05 (s, 3H, N-CH$_3$), 3.12-3.25 (mc, 2H, Ph-C$\underline{H}_2$), 3.27-3.40 (mc, 2H, Ph-C$\underline{H}_2$), 3.86 (s, 3H, O-C$\underline{H}_3$), 3.86-4.10 (mc, 4H, Ph-CH$_2$-C$\underline{H}_2$), 7.11-7.22 (s, 1H, arom., H1), 7.35-7.60 (m, 5H, arom.); ^{13}C-NMR (**6c**, MeOD): 23.86 (Ph-$\underline{C}H_2$), 24.71 (Ph-$\underline{C}H_2$), 45.55 (N-$\underline{C}H_3$), 54.58 (Ph-CH$_2$-$\underline{C}H_2$), 54.75 (Ph-CH$_2$-$\underline{C}H_2$), 56.71 (O-$\underline{C}H_3$), 98.66 (C-OH), 113.34 (C1), 124.73 (C3), 125.73 (C13), 128.55 (C12), 129.65 (arom.), 130.63 (arom.), 131.28 (arom.), 131.75 (arom.), 131.78 (arom., quat.), 134.52 (C13c), 134.54 (C9a), 155.55 (C2); IR (**3c**, KBr, cm^{-1}): 3436, 2928, 2845, 1658, 1596, 1486, 1274; MS (EI): m/z (% rel. Int.) = 329 (M^+, 26.4), 314(3.4), 300(6.9), 285(20.0), 271(6.5), 255(9.1), 243(14.6), 223(19.3), 208(25.7), 197(6.2), 189(6.4), 178(16.6), 165(23.1), 146(38.0), 132(6.6), 115(8.9), 103(10.9), 89(14.9), 77(14.6), 71(100.0), 58(31.7); Anal. Calcd for (**3c**): $C_{19}H_{20}NO_2Cl$ x $^4/_5$ H_2O: C, 66.3; H, 6.3; N, 4.0. Found: C, 66.2; H, 6.0; N, 3.9.

9. A. J. Kirby and C. J. Logan, *J. Chem. Soc., Perkin Trans. 2*, 1978, 642.
10. K. Torssell, *Tetrahedron Lett.*, 1966, **37**, 4445.
11. N. J. Leonard and M. Oki, *J. Am. Chem. Soc.*, 1955, **77**, 6241.
12. F. R. Stermitz, R. M. Coomes, and D. R. Harris, *Tetrahedron Lett.*, 1968, **36**, 3915.
13. P. T. Lansbury, *J. Am. Chem. Soc.*, 1961, **83**, 429.
14. H. B. Bürgi, J. D. Dunitz, and E. Shefter, *J. Am. Chem. Soc.*, 1973, **95**, 5065.
15. M. Decker and J. Lehmann, *Arch. Pharm. Pharm. Med. Chem.*, 2003, **336**, 466.