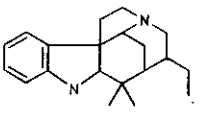
A NEW SYNTHETIC ROUTE TO THE TETRACYCLIC FRAMEWORK OF STRYCHNOS ALKALOIDS *VIA* INTRAMOLECULAR ALDOL REACTION

Süleyman Patir*[a], Peter Rosenmund[b], and Peter H. Götz[c]

[a]Department of Science, Faculty of Education, Hacettepe University, TR-06525 Beytepe-Ankara, Turkey
[b]Institut für Organische Chemie, J.-W.-Goethe-Universität Frankfurt, Theodor-Stern-Kai 7, D-60596 Frankfurt/Main, Germany
[c]Fachbereich MND, Fachhochschule Gießen-Friedberg, Wilhelm-Leuschner-Straße 13, D-61169 Friedberg, Germany

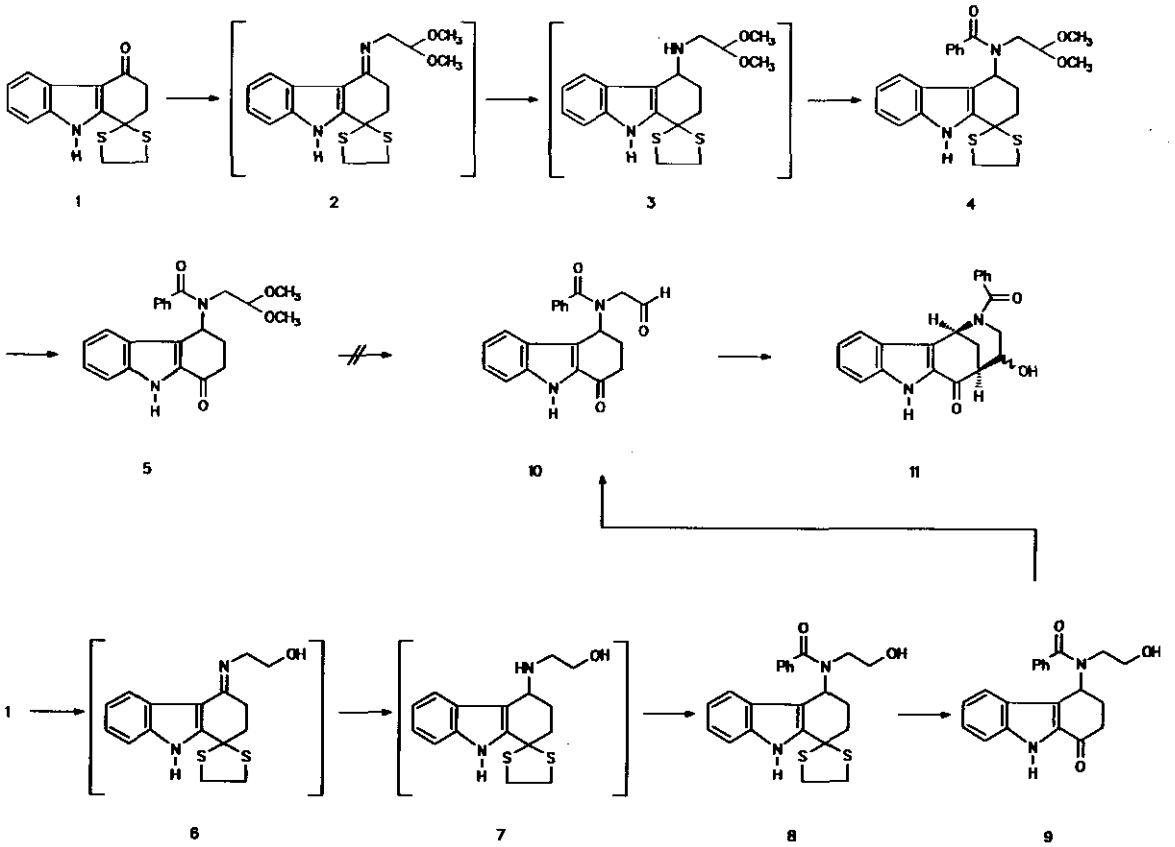
Abstract - By treatment of 2,3,4,9-tetrahydrospiro[1*H*-carbazole-1,2'-[1,3]dithiolan]-4(9*H*)-one (1) with ethanolamine, followed by reduction of the corresponding imine (6) with $NaBH_4$ to the amine (7) and benzoylation, *N*-benzoyl-*N*-(2-hydroxyethyl)-{2,3,4,9-tetrahydrospiro-[1*H*-carbazole-1,2'-(1,3)dithiolan]-4-yl}amine (8) is formed, which can be deprotected to 4-[Benzoyl-(2-hydroxyethyl)amino]-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (9). Oxidation of the primary hydroxyl group yields [*benzoyl*-(1-oxo-2,3,4,9-tetrahydrocarbazol-1-one-4-yl)amino]acetaldehyde (10), a key-intermediate for the cyclization to 2-benzoyl-4-hydroxy-1,2,3,4,5,7-hexahydro-1,5c-methanoazocino[4,3-*b*]indol-6-one (11), which represents the tetracyclic skeleton of Strychnos-type alkaloids.

Most of the routes to the tetracyclic substructures of the Strychnos-type alkaloids which have been reported in the literature[1] start with the aromatic A- and a heterocyclic D-ring and build up the complete system by closing the other rings later.



Strychnan-type skeleton

In this paper we describe a synthetic strategy utilising a *N*-substituted 1-oxo-4-aminotetrahydrocarbazole (carbazole numbering) as a key-intermediate.



This tricyclic compound containing the rings A, B and C allows an intramolecular closure of the D-ring by aldol reaction in the last synthetic step, yielding the tetracyclic skeleton of many indole alkaloids. For the preparation of the open chain precursor (10) we developed a simple route using mild reaction conditions and easily

available starting materials.

To get the aldehyde (10) we studied two different routes: the first is proceeding from 1[2] to form the instable imine (2)[3] by reaction with aminoacetaldehyde dimethylacetal/$SnCl_2$ in benzene, which can be reduced to amine (3) with $NaBH_4$ without isolation and trapped by acylation with benzoyl chloride to form 4. Cleavage of the thioketal[4] of 4 with benzeneseleninic anhydride gives 5 in good yield. Unfortunately all attempts to cleave the acetal group of 5 to get the desired aldehyde (10) failed and yielded only decomposition products. So we tried a second way. We converted 1 into 6 using ethanolamine and $FeCl_3$ as catalyst. Without isolation of the instable imine (6) we reduced it with $NaBH_4$ and trapped the resulting amine with benzoyl chloride to form the amide (8). Cleavage of the ketal group of 8 with benzeneseleninic anhydride gives 9, which can be oxidized to 10 using oxalyl chloride/DMSO at -60°C.[5] 10 can be cyclized under mild conditions by intramolecular aldol reaction using NaH as base. The tetracyclic compound (11) is formed as a mixture of the epimeric alcohols.

ACKNOWLEDGEMENT

This investigation was supported by the "DAAD" (Deutscher Akademischer Austauschdienst).

EXPERIMENTAL

Melting points (uncorrected): Copper block. ^{1}H-Nmr: Bruker WH-270 and WH-300, internal standard TMS. - Ms: IMS-HX 110. - Ir: Hitachi 270-30. - Chromatography: Thin-layer: 0.25 mm Silica gel plates 60 F 254, Merck. - Column chromatography: Silica gel 70-230 mesh (0.063-0.2 mm), Merck.

N-Benzoyl-*N*-(2,2-dimethoxyethyl)-{2,3,4,9-tetrahydrospiro[1*H*-carbazole-1,2'-(1,3)dithiolan]-4-yl}amine (4): 2.0 g (7.26 mmol) of 2,3,4,9-tetrahydrospiro[1*H*-carbazole-1,2'-[1,3]dithiolan]-4(9*H*)-one (1), 3 ml (27.5 mmol) of aminoacetaldehyde dimethylacetal and 1.1 g (8 mmol) of $SnCl_2$ in 70 ml of benzene are heated for 7 h using a water trap. The progress of the reaction is monitored by tlc. When the reaction is complete, the solvent is evaporated. The residue is dissolved in methanol/THF (1:1) and cooled in an ice bath. Under stirring 1.5 g (40 mmol) of $NaBH_4$ are added in several portions. The ice bath is removed and the mixture is stirred for 6 h under nitrogen atmosphere. After this the solvent is evaporated under reduced pressure and the residue is dissolved in ether. After washing with 20 ml of 10% NaOH the organic layer is dried with $MgSO_4$ and the solvent is evaporated. The residue is dissolved in 30 ml of $CHCl_3$ and 2 ml (14.4 mmol) of triethylamine and 2 ml (17.2 mmol) of benzoyl chloride are added. The mixture is allowed to stir for 30 min at room temperature. Then washing with 20 ml of 10% NaOH follows. The organic layer is dried with $MgSO_4$ and the solvent is evaporated under reduced pressure. The residue is chromatographed using silica gel and toluene/ethyl acetate (2:1). After evaporation of the solvent 1.82 g (55%) of the pure product are isolated. mp 209°C (ethyl acetate). Tlc: R_f = 0.54 (benzene/ethyl acetate 1:2). - ^{1}H-Nmr ($CDCl_3$, 300 MHz): δ = 2.16-2.33 (m; 2H), 2.46-2.60 (m; 2H), 2.82-2.91 (m; 1H), 3.30-3.62 (m; 10 H, $-OCH_3$, $S-CH_2-CH_2-S$), 3.70-3.77 (m; 1H), 4.89-4.93 (m; 1H), 5.12-5.29 (m; 1H), 7.03-7.44 (m; 7H, aromat.), 7.56-7.59 (m; 2H, aromat.), 8.41 (s; 1H, NH). - Ir (KBr): ν = 3330 cm^{-1} (NH), 1630 (C=O). Anal. Calcd for $C_{25}H_{28}N_2O_3S_2$: C, 64.08; H, 6.02; N, 5.98. Found: C, 63.92; H, 6.17; N 6.21.

4-[Benzoyl-(2,2-dimethoxyethyl)amino]-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (5): 1.6 g (3.53 mmol) of the thioketal (4) and 1.44 g (4 mmol)

of benzeneseleninic anhydride are dissolved in 30 ml of $CHCl_3$. 1.0 ml (12.4 mmol) of pyridine is added. The mixture is stirred under nitrogen atmosphere at room temperature. After 40 h washing with 20 ml of 10% NaOH follows. The organic layer is dried with $MgSO_4$ and the solvent is removed under reduced pressure. The residue is purified by chromatography using silica gel and toluene/ethyl acetate (2:1). 0.965 g (69%) of the product are isolated. mp 208°C (ethyl acetate). Tlc: R_f = 0.32 (toluene/ethylacetate 1:1). - ^{1}H-Nmr ($CDCl_3$, 300 MHz): δ = 2.35-2.56 (m; 2H), 2.67-2.87 (m; 3H), 3.40 (s; 3H, OCH_3), 3.50 (s; 3H, OCH_3), 3.93 (d; 1H, J = 12.78 Hz), 4.89 (d; 1H, J = 5.75 Hz), 5.43 (d; 1H, J = 8.9 Hz), 7.14-7.28 (m; 1H, aromat.), 7.33-7.50 (m; 5H, aromat.), 7.54-7.60 (m; 3H, aromat.), 9.42 (s; 1H, NH). - Ir (KBr): ν = 3320 cm^{-1} (NH), 1670 (C=O, ketone), 1617 (C=O, amide). Anal. Calcd for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.56; H, 6.29; N, 6.98.

N-Benzoyl-*N*-(2-hydroxyethyl)-{2,3,4,9-tetrahydrospiro[1*H*-carbazole-1,2'-(1,3)dithiolan]-4-yl}amine (8): 3.0 g (10.89 mmol) of 2,3,4,9-tetrahydrospiro-[1*H*-carbazole-1,2'-[1,3]dithiolan]-4(9*H*)-one (1), 10 ml (162 mmol) of aminoethanol and 2.1 g (13 mmol) of $FeCl_3$ in 100 ml of benzene are heated for 24 h using a water trap. Then the solvent is evaporated, the residue is dissolved in 50 ml methanol/THF (1:1) and cooled in an ice bath. Under stirring 2.5 g (65 mmol) of $NaBH_4$ are added in several portions. The ice bath is removed and the mixture is stirred for 6 h under nitrogen atmosphere. After this 50 ml of 10% NaOH are added and the mixture is extracted three times with 50 ml of ethyl acetate. The combined organic layers are dried with $MgSO_4$ and the solvent is evaporated. The residue is dissolved in 50 ml of $CHCl_3$ and 3 ml (21.6 mmol) of triethylamine and 3 ml (25.8 mmol) of benzoyl chloride are added. The mixture is allowed to stir for 10 min at room temperature. Washing with 20 ml of 10% NaOH follows. The

organic layer is dried with $MgSO_4$ and evaporated under reduced pressure. The residue is chromatographed using silica gel and toluene/ethyl acetate (1:1). After evaporation of the solvent 2.20 g (47%) of the pure product are isolated. mp 221°C (ethyl acetate). Tlc: R_f = 0.24 (toluene/ethyl acetate 1:1). - ^{1}H-Nmr ($CDCl_3$/DMSO-d6 1:1, 300 MHz): δ = 2.14-2.58 (m; 4H), 3.04-3.59 (m; 4H), 3.65-3,51 (m; 4H), 4.44 (t; 1H, J = 5.22, OH), 5.12-5.18 (m; 1H), 7.02-7.59 (m; 9H), 10.21 (s; 1H, NH). - Ir (KBr): ν = 3400 cm^{-1} (OH), 3200 (NH), 1619 (C=O). Anal. Calcd for $C_{23}H_{24}N_2O_2S_2$: C, 65.07; H, 5.70; N, 6.60. Found C, 65.23; H, 5.90; N, 6.47.

4-[Benzoyl-(2-hydroxyethyl)amino]-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (9): 2.50 g (5.88 mmol) of the thioketal (8) and 2.34 g (6.5 mmol) of benzeneseleninic anhydride are dissolved in 50 ml of $CHCl_3$. 2.0 ml (24,8 mmol) of pyridine are added. The mixture is stirred under nitrogen atmosphere at room temperature. After 48 h washing with 20 ml of 10% NaOH follows. The organic layer is dried with $MgSO_4$ and the solvent is removed under reduced pressure. After crystallization from ether 1.26 g (62%) of the product are isolated. mp 207°C (ether). Tlc: R_f = 0.54 (ethyl acetate). - ^{1}H-Nmr (DMSO-d6, 300 MHz): δ = 2.21-2.23 (m; 2H), 2.14-2.45 (m; 1H), 2.70-2.75 (m; 1H), 3.34-3.74 (m: 4H), 4.72 (t; J = 5.5 Hz, OH), 5.00 (t; J = 7.0 Hz, 1H), 7.00-7.55 (m; 9H, aromat.), 11.10 (s; 1H, NH). - Ir (KBr): ν = 3440 cm^{-1} (OH), 3200 (NH), 1650 (C=O ketone) 1620 (C=O amide). Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.13; H, 5.80; N, 7.86.

[Benzoyl-(1-oxo-2,3,4,9-tetrahydrocarbazol-1-one-4-yl)amino]acetaldehyde (10): 20 ml of CH_2Cl_2 and 0.36 ml (2 mmol) of oxalyl chloride are cooled to -60°C and 0.30 ml (4 mmol) of dimethyl sulfoxide are added. After stirring for 10 min 0.50 g (1.43 mmol) of alcohol (9), dissolved in 10 ml of CH_2Cl_2 and 5 ml of DMSO, is added slowly and the

mixture is stirred for 45 min. Finally 1.96 g (14 mmol) of triethylamine are added and the mixture is allowed to warm up to room temperature. 10 ml of $CHCl_3$ are added and extraction with three portions of $CHCl_3$ (30 ml each) follows. The combined organic layers are dried with $MgSO_4$ and the solvent is evaporated. After crystallization of the residue 0.36 g (72%) of the product are isolated. mp 211°C (THF/ethyl acetate). Tlc: R_f = 0.42 (toluene/ethyl acetate 1:1). - ^{1}H-Nmr (DMSO-d6, 270 MHz): δ = 2.32-2.38 (m; 2H), 2.45-2.73 (m; 2H), 3.78 (d; J = 17.9 Hz, 1H), 4.15 (d; J = 17.6 Hz, 1H), 5.46 (t; J = 7.6 Hz, 1H), 7.17-7.71 (m; 9H, aromat.), 9.50 (s; 1H, CHO), 11.96 (s; 1H, NH). - Ir (KBr): ν = 3260 cm^{-1} (NH), 1732 (C=O, aldehyde), 1660 (C=O, ketone), 1619 (C=O, amide). Anal. Calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.66; H, 5.34; N 7.86.

2-Benzoyl-4-hydroxy-1,2,3,4,5,7-hexahydro-1,5c-methanoazocino[4,3-*b*]-indol-6-one (11): 0.35 g (0.86 mmol) of NaH (60% dispersion in oil) and 0.15 g (0.43 mmol) of the aldehyde (10) are dissolved in 30 ml of tetrahydrofuran and the mixture was stirred under nitrogen atmosphere for 3 h at 50°C. Then the mixture is cooled in an ice bath and 5 ml of 5% HCl are added. After extraction with 30 ml of $CHCl_3$ the organic layer is washed with 10 ml of 5% $NaHCO_3$ solution, dried with $MgSO_4$ and the solvent is evaporated. After purification of the residue by chromatography using silica gel and ethyl acetate/$CHCl_3$ (3:1) 0.087 g (58%) of 11 (mixture of epimeric alcohols) are isolated. mp 285°C (decomp.) (acetone). Tlc: R_f = 0.24 (ethyl acetate/$CHCl_3$ 3:1). - ^{1}H-Nmr ($CDCl_3$, 270 MHz): δ = 2.26 (d; J = 13.06 Hz, 1H), 2.64-2.74 (t; 2H, J = 11.9 Hz), 2.79 (s; 1H, OH), 3.11 (s; 1H), 3.77 (t; J = 6.4 Hz, 1H), 4.12 (d; J = 5.15 Hz, 1H), 6.44 (m; 1H), 7.08-7.67 (m; 8H, aromat.), 7.97 (d; J = 7.6 Hz, 1H), 9.34 (s; 1H, NH). - Ir (KBr): ν = 3570 cm^{-1} (OH), 3170 (NH), 1670 (C=O, ketone), 1616 (C=O, amide). -

Ms: 346 (57) [M^+], 225 (5), 213 (32), 184 (100), 166 (10), 154 (7), 105 (29), 77 (16). Anal. Calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.54; H, 5.28; N 8.16.

REFERENCES

1 J. Bonjoch, J. Quirante, A. Linares, and J. Bosch, *Heterocycles*, 1988, **27**, 2883; M. Alvarez, R. Lavilla, and J. Bosch, *Tetrahedron Lett.*, 1987, **28**, 4457; M. Feliz, J. Bosch, D. Mauleon, M. Amat, and A. Domingo, *J. Org. Chem.*, 1982, **47**, 2435; J. Bonjoch, J. Quirante, M. Rodriguez, and J. Bosch, *Tetrahedron*, 1988, **44**, 2078; H.-J. Teuber, C. Tsaklakidis, and J. W. Bats, *Liebigs Ann. Chem.*, 1992, 461; H. Fritz, M. Soleymani-Jamarani, J. W. Bats, and H.-J.Teuber, *Liebigs Ann. Chem.*, 1993, 705; P. Magnus, N. L. Sear, C. S. Kim, and N. Vicker, *J. Org. Chem.*, 1992, **57**, 70.

2 Previous publication in this series: S. Patir, and P. H. Götz, *Liebigs Ann. Chem.*, 1993, 1323.

3 R. W. Layer, *Chem. Rev.*, 1963, **63**, 489.

4 N. J. Cussons and S. v. Ley, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1654.

5 A. J. Mancuso, S.-L. Huang, and D.Swern, *J. Org. Chem.*, 1978, **43**, 2480.

Received, 6th February, 1995