Synthesis of the Azocino[4,3-*b*]indole Core Structure for the Synthesis of Strychnos Alkaloids

Yavuz Ergün[a], Süleyman Patir[b] and Gürol Okay[a]*

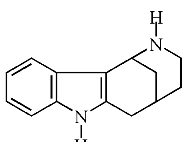
[a]Department of Chemistry, Faculty of Science, Hacettepe University, 06532-Beytepe-Ankara, Turkey
[b]Department of Science, Faculty of Education, Hacettepe University, 06532-Beytepe-Ankara, Turkey

Received August 17, 2001

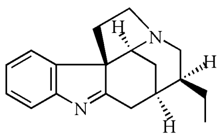
The synthesis of compound **12** which has a hexahydro-1,5-methanoazocino[4,3-*b*]indole structure for the synthesis of pentacyclic strychnos type alkaloids (tubifolin and tubifolidine) is described. Many new compounds **5-12** have also been synthesized.

J. Heterocyclic Chem., **39**, 315 (2002).

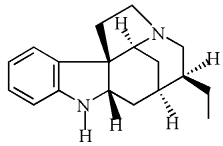
The tetracyclic structure hexahydro-1,5-methanoazocino[4,3-*b*]indole (**1**) is the core structure for the synthesis of pentacyclic strychnos type of alkaloids such as tubifolin (**2**) and tubifolidine (**3**) [1,2,3]. Therefore, many chemists have tried to synthesize this tetracyclic ring system [4,5,6].



1

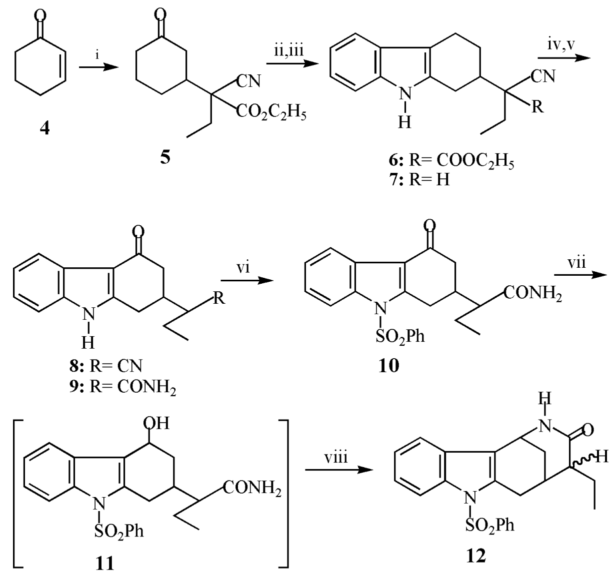


2



3

In this work we have succesfully obtained compound **12** which has a hexahydro-1,5-methanoazocino[4,3-*b*]indole structure. In the first part of the work a new cyclohexanone derivative **5** was obtained by the reaction of 2-cyclohexenone with ethyl 2-cyano butanoate by a Michael reaction [7]. Reaction of compound **5** with phenyl hydrazine by Fischer indol reaction gave the tetrahydrocarbazole derivative **6** [8]. Compound **7** which was obtained by deesterification of **6** at high temperature, was oxidized using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone yielding compound **8** [9]. Subsequent hydrolysis of **8** with boron fluoride in aqueous acetic acid afforded compound **9** [10]. We also tried to obtain amide **9** from nitrile **8** using hydrogen peroxide-sodium hydroxide [11]. Unfortunately the trial was unsuccessful. Later we protected the indol nitrogen using tetrabutyl ammonium hydrogen sulfate and benzene sulfonyl chloride, which resulted in compound **10**, which was reacted with sodium borohydride to yield intermediate **11** [6]. Finally, hexahydro-1,5-methanoazocino[4,3-*b*]indole structure **12** was synthesized by ring closure of **11** using trifluoro acetic acid [6].



Reagents and Conditions: (i) $CH_3CH_2CHCNCO_2C_2H_5$, NaOEt/EtOH, 0¡, 15 min, then rt, 16h, 66%; (ii) $PhNHNH_2$, AcOH, N_2, reflux, 5h, 57%; (iii) DMSO, NaCl, H_2O, 160°, 18h, 68%; (iv) DDQ, THF (90%), rt, 5h, 52%; (v) $BF_3.Et_2O$, AcOH-H_2O, reflux, 72h, 75%; (vi) TBAHS, NaOH (50%), CH_2Cl_2, $PhSO_2Cl$, rt, 1h, 84%; (vii) $NaBH_4$, THF-MeOH, rt, 2h, 86%; (viii) CF_3CO_2H, CH_2Cl_2, 0¡ then rt, 12h, 36%.

EXPERIMENTAL

All melting points were measured in sealed tubes using an electrothermal digital melting point apparatus (Gallenkamp) and are uncorrected. Infrared spectra were recorded on a Hitachi 270-30 infrared spectrometer. ^{1}H-nmr spectra were obtained on a high resolution fourier transform Bruker WH-400 NMR spectrometer with tetramethylsilane as an internal stantard. Mass spectra were recorded on a Micromass UK Platform II LC-MS spectrometer. Analytical and preparative thin layer chromatography (TLC) was carried out using silica gel 60 HF-254 (Merck). Column chromatography was carried out by using 70-230 mesh silica gel (0.063-0.2 mm, Merck).

Ethyl 2-Cyano-2-(3-oxo-cyclohexyl)-butanoate (**5**).

To a solution of a catalytic amount of sodium ethylate in ethanol (prepared by adding 1 g of metallic sodium to 50 ml of absolute ethanol at 0°) were added 20 g (14 mmoles) of ethyl

2-cyano butanoate, and the solution was stirred for 15 minutes at 0°. To this solution were added dropwise 12.5 g (13 mmoles) of 2-cyclohexene-1-one at the same temperature. The reaction mixture was stirred for 16 hours at room temperature. The solution was acidified with acetic acid, then diluted with water. The compound was extracted with ether, and the extract was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and destillation of the residue gave 20.5 g (66%) of **5**, bp: 135-145° (5 mmHg); ir (potassium bromide): ν 2965 (CH), 2250 (CN), 1740 (C=O) 1685 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.11 (3H, t, J = 7.4 Hz, CH_2CH_3), 1.33 (3H, t, J = 7.2 Hz, OCH_2CH_3), 1.60-1.80 (2H, m, CH_2), 1.90 (2H, q, J = 7.4 Hz, CH_2CH_3), 1.95-2.10 (2H, m, CH_2), 2.30-2.42 (5H, m, CH and $2xCH_2$), 4.25 (2H, q, J = 7.1 Hz, OCH_2CH_3); ms: m/z 238(1.5) $[M+1]^+$, 237(1.1) $[M]^+$, 210(1.15) $[M-HCN]^+$, 182(1.50) $[M-C_3H_5N]^+$, 181(1.60) $[M-C_3H_6N]^+$, 153(1.64) $[M-C_3H_{10}N]^+$, 141(22) $[M-C_6H_9O]^+$, 113(28) $[M-C_8H_{12}O]^+$, 97(82) $[M-C_7H_{10}NO_2]^+$, 96(100) $[M-C_7H_{11}NO_2]^+$, 69(67) $[M-C_9H_{11}O_3]^+$, 68(100) $[M-C_9H_{12}O_3]^+$.

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.82; H, 8.02; N, 5.91. Found: C, 65.75; H, 8.06; N, 5.85.

Ethyl 2-Cyano-2-(1, 2, 3, 4-tetrahydrocarbazol-2-yl)-butanoate (**6**).

A solution of 10 g (42.2 mmoles) of **5** and 4.6 g (42.5 mmoles) of phenyl hydrazine in 250 ml of acetic acid was refluxed for 5 hours under N_2 and then cooled to room temperature. The reaction mixture was poured into 500 ml of cold water and extracted with ether. The organic layer was washed with 100 ml of 10% hydrochloric acid and then 100 ml of 10% sodium carbonate. The organic layer was dried with anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The crude product was dissolved in chloroform and chromatographed using silica gel and ethyl acetate. The solvent was evaporated and the residue was recrystallized from methanol to yield 7.5 g (57%) of **6**, mp: 158-159°; rf: 0.64 (ethyl acetate); ir (potassium bromide): ν 3415 (NH), 2940 (CH), 2250 (CN) 1745 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.11 (3H, t, J = 7.4 Hz, CH_2CH_3), 1.35 (3H, t, J = 7.1 Hz, OCH_2CH_3), 1.90-2.80 (9H, m, CH and $4xCH_2$), 4.25-4.35 (2H, q, J = 7.1 Hz, OCH_2CH_3), 7.05-7.12 (2H, m, aromatic protons), 7.20 (1H, d, J = 8.1 Hz, aromatic proton), 7.45 (1H, d, J = 7.5 Hz, aromatic proton), 7.80 (1H, s, NH); ms: m/z 311(5) $[M+1]^+$, 310(22) $[M]^+$, 265(4) $[M-OC_2H_5]^+$, 238(4) $[M-CO_2C_2H_4]^+$, 237(3) $[M-CO_2C_2H_5]^+$, 170(59) $[M-C_7H_{10}NO_2]^+$, 169(75) $[M-C_7H_{11}NO_2]^+$, 143(100) $[M-C_9H_{13}NO_2]^+$, 69(31) $[M-C_{15}H_{15}NO_2]^+$, 68(26.5) $[M-C_{15}H_{16}NO_2]^+$.

Anal. Calcd. for $C_{19}H_{22}N_2O_2$: C, 73.55; H, 7.10; N, 9.03. Found: C, 73.61; H, 7.02; N, 9.15.

2-(1, 2, 3, 4-Tetrahydrocarbazol-2yl)-butyronitrile (**7**).

A solution of 7 g (22.6 mmoles) of **6**, 3.96 g (67.74 mmoles) of sodium chloride and 1.22 g (67.74 mmoles) of water in 100 ml of dimethyl sulfoxide was stirred for 18 hours at 160°. Then the mixture was poured into 250 ml of cold water and extracted with ether. The organic layer was dried with anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel using ethyl acetate. After the solvent was evaporated, the product was recrystallized from methanol to yield 3.65 g (68%) of **7**, mp: 167-168°; rf: 0.60 (ethyl acetate); ir (potassium bromide): ν 3400 (NH), 2980 (CH), 2255 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.13 (3H, t, J = 7.3 Hz, CH_2CH_3), 1.46-1.80 (4H, m, $2xCH_2$), 1.85-2.05 (2H, m, CH_2) 2.59-2.66 (1H, m, CH), 2.74-2.82 (2H, m, CH_2), 2.98 (1H, m, CH), 7.12 (1H, m, J = 7.5 Hz, aromatic proton), 7.23 (1H, m, J = 7.6 Hz, aromatic proton), 7.35 (1H, d, J = 8.1 Hz, aromatic proton), 7.54 (1H, d, J = 8.1 Hz, aromatic proton), 8.14 (1H, s, NH); ms: m/z 240(5) $[M+2]^+$, 239(25.5) $[M+1]^+$, 238(3) $[M]^+$, 210(2.78) $[M-C_2H_4]^+$, 207(1.78) $[M-C_2H_7]^+$, 170(9.55) $[M-C_4H_6N]^+$, 169(9.46) $[M-C_4H_7N]^+$, 168(29) $[M-C_4H_8N]^+$, 167(20.14) $[M-C_4H_9N]^+$, 117(5.38) $[M-C_8H_{11}N]^+$, 115(19) $[M-C_8H_{13}N]^+$, 77(11) $[M-C_{10}H_{13}N_2]^+$.

Anal. Calcd. for $C_{16}H_{18}N_2$: C, 80.68; H, 7.56; N, 11.76. Found: C, 80.60; H, 7.58; N, 11.79.

2-(1, 2, 3, 4-Tetrahydrocarbazol-4-oxo-2yl)-butyronitrile (**8**).

To a solution of 5 g (21 mmoles) of **7** in 50 ml of tetrahydrofurane (90%) were added dropwise 9.54 g (42 mmoles) of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in 15 ml of tetrahydrofurane at 0°. The reaction mixture was stirred for 5 hours at room temperature then the solution was poured into 500 ml of 10% sodium hydroxide and extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, and the solvent was removed. The residue was purified by chromatography using silica gel and ethyl acetate. After the solvent was evaporated, the product was recrystallized from ether to afford 2.75 g (52%) of **8**, mp: 224-225°; rf: 0.32 (ethyl acetate); ir (potassium bromide): ν 3300 (NH), 2980 (CH), 2250 (CN), 1645 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.17 (3H, t, J = 7.3 Hz, CH_3), 1.76 (2H, m, CH_2), 2.58-2.75 (4H, m, $2xCH_2$), 3.03 (1H, m, CH), 3.25 (1H, m, CH), 7.28 (2H, m, aromatic protons), 7.37 (1H, d, J = 8.8 Hz, aromatic proton), 8.21 (1H, d, J = 8.7 Hz, aromatic proton), 8.65 (1H, s, NH); ms: m/z 254(7.35) $[M+2]^+$, 253(36) $[M+1]^+$, 252(12) $[M]^+$, 185(4.10) $[M-C_4H_5N]^+$, 184(25) $[M-C_4H_6N]^+$, 183(5.78) $[M-C_4H_7N]^+$, 158(13) $[M-C_5H_4NO]^+$, 157(100) $[M-C_5H_5NO]^+$, 156(31) $[M-C_5H_6NO]^+$, 131(6.93) $[M-C_7H_7NO]^+$, 130(54.5) $[M-C_7H_8NO]^+$, 129(23) $[M-C_7H_9NO]^+$, 128(42.5) $[M-C_7H_{10}NO]^+$, 117(3.83) $[M-C_8H_9NO]^+$, 104(1.94) $[M-C_8H_8N_2O]^+$, 103(13.5) $[M-C_8H_9N_2O]^+$, 102(48.5) $[M-C_8H_{10}N_2O]^+$, 77(21) $[M-C_{10}H_{11}N_2O]^+$.

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.19; H, 6.35; N, 11.11. Found: C, 76.23; H, 6.37; N, 11.15.

2-(1, 2, 3, 4-Tetrahydrocarbazol-4-oxo-2yl)-butanamide (**9**).

A solution of 1.5 g (5.95 mmoles) of **8**, 4.22 g (29.75 mmoles) of boron trifluoride-diethyl ether complex and 0.10 g (5.59 mmoles) of water in 50 ml of acetic acid was refluxed for 72 hours. Then the mixture was poured into 10% sodium hydroxide solution and extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel using ethyl acetate. After the solvent was evaporated, the product was recrystallized from methanol to yield 1.20 g (75%) of **9**, mp: 192-193°; rf: 0.41 (ethyl acetate); ir (potassium bromide): ν 3405 (NH), 3395 (NH), 2980 (CH), 1690 (C=O), 1665 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.20 (3H, t, J = 7.3 Hz, CH_3), 1.80 (2H, m, CH_2), 2.60-2.80 (4H, m, $2xCH_2$), 3.05 (1H, m, CH), 3.30 (1H, m, CH), 5.40 (1H, s, NH), 7.32 (2H, m, aromatic protons), 7.42 (1H, d, J = 9.0 Hz, aromatic proton), 8.24 (1H, d, J = 9.1 Hz, aromatic proton) 8.70 (1H, s, NH); ms: m/z 271(1.5) $[M+1]^+$, 270(5) $[M]^+$, 254(2) $[M-NH_2]^+$, 226(1.07) $[M-CONH_2]^+$, 185(2.96) $[M-C_4H_7NO]^+$, 184(8.45) $[M-C_4H_8NO]^+$, 183(6.31) $[M-C_4H_9NO]^+$, 170(43)

$[M-C_4H_6NO_2]^+$, 169(71) $[M-C_4H_7NO_2]^+$, 168(100) $[M-C_4H_8NO_2]^+$, 167(73) $[M-C_4H_9NO_2]^+$, 131(20) $[M-C_7H_9NO_2]^+$, 130(45) $[M-C_7H_{10}NO_2]^+$, 129(50) $[M-C_7H_{11}NO_2]^+$, 128(45) $[M-C_7H_{12}NO_2]^+$, 118(47) $[M-C_8H_{10}NO_2]^+$, 117(47) $[M-C_8H_{11}NO_2]^+$, 93(23) $[M-C_{10}H_{11}NO_2]^+$, 92(14) $[M-C_{10}H_{12}NO_2]^+$, 91(62) $[M-C_{10}H_{13}NO_2]^+$, 77(55) $[M-C_{10}H_{13}N_2O_2]^+$.

Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.11; H, 6.67; N, 10.37. Found: C, 71.04; H, 6.60; N, 10.41.

2-(1,2,3,4-Tetrahydrocarbazol-4-oxo-9-benzenesulfonyl-2-yl)-butanamide (**10**).

A solution of 1.25 g (4.63 mmoles) of **9** in 50 ml of dichloromethane was cooled to 0°. After that 5 ml of 50% sodium hydroxide, 100 mg of tetrabuthylammonium hydrogen sulfate and 0.83 g (4.70 mmoles) of benzene sulfonyl chloride was added, and the mixture stirred for 1 hour at room temperature, washed with 50 ml of 10% hydrochloric acid, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the resulting residue was chromatographed using silica gel and ethyl acetate. The solvent was removed and then the product was recrystallized from ether to afford 1.6 g (84%) of **10**, mp: 278-281°; rf: 0.49 (ethyl acetate); ir (potassium bromide): ν 3400 (NH), 2980 (CH), 1695 (C=O), 1665 (C=O), 1350 and 1170 (S=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.05 (3H, m, J = 7.3 Hz, CH_3), 1.72-1.82 (2H, m, CH_2), 1.86-1.90 (2H, m, CH_2), 2.15-2.25 (2H, m, CH_2), 2.85-2.95 (1H, m, CH), 3.40-3.50 (1H, m, CH), 5.40 (2H, bs, NH_2), 7.10 (1H, d, J = 8.9 Hz, aromatic proton), 7.15-7.40 (4H, m, aromatic protons), 7.45 (1H, d, J = 8.9 Hz, aromatic proton), 7.55 (1H, d, J = 9.0 Hz, aromatic proton), 7.80-7.90 (2H, m, aromatic protons); ms: m/z 411(3) $[M+1]^+$, 410(9) $[M]^+$, 409(25) $[M-H]^+$, 325(10) $[M-C_4H_7NO]^+$, 324(7) $[M-C_4H_8NO]^+$, 269(17) $[M-C_6H_5SO_2]^+$, 141(86) $[M-C_{16}H_{17}N_2O_2]^+$, 77(100)) $[M-C_{16}H_{17}N_2SO_4]^+$.

Anal. Calcd. for $C_{22}H_{22}N_2SO_4$: C, 64.39; H, 5.36; N, 6.83. Found: C, 64.45; H, 5.40; N, 6.75.

4-Ethyl-2, 3, 4, 5, 6, 7-hexahydro-1,5-methano-3-oxo-7-(benzene sulfonyl)-2*H* azocino[4,3-*b*]indole (**12**).

A solution of 1 g (2.4 mmoles) of **10** in 10 ml of methanol-tetrahydrofurane (1:1) was cooled to 0° and treated with 18 mg (4.8 mmoles) of sodium borohydride and the mixture stirred for 2 hours at room temperature. The reaction mixture was diluted water and extracted with chloroform. The organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated to yielded 0.87 g of an oily crude product **11**. After that, 0.75 g (1.82 mmoles) of **11** were dissolved in 15 ml of dichloro methane and cooled to 0°. The reaction mixture was treated with 0.23 g (2 mmoles) of trifluoro acetic acid and stirred for 12 hours at room temperature. After 12 hours the reaction mixture was poured into water and extracted with dichloromethane. The organic layer was dried with anhydrous magnesium sulfate and the solvent was evaporated. The crude product was chromatographed with silica gel and ethyl acetate. The solvent was removed under reduced pressure and the product was recrystallized from methanol to afford 0.35 g (36%) of **12**, mp: 197-198°; rf: 0.30 (ethyl acetate); ir (potassium bromide): ν 3350 (NH), 2980 (CH), 1670 (C=O), 1325 and 1175 (S=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.90 (3H, m, J = 7.2 Hz, CH_3), 1.25-1.50 (3H, m, CH and CH_2), 1.75-2.00 (2H, m, CH_2), 2.45-2.65 (2H, m, CH_2), 2.75 (1H, m, CH), 3.10 (1H, m, CH), 4.80 (1H, bs, NH), 6.85 (1H, d, J = 9.1 Hz, aromatic proton), 7.10 (2H, m, aromatic protons), 7.20-7.70 (4H, m, aromatic protons), 7.85-7.95 (2H, m, aromatic protons); ms: m/z 395(1.5) $[M+1]^+$, 394(4.5) $[M]^+$, 254(12) $[M-C_6H_4SO_2]^+$, 253(12) $[M-C_6H_5SO_2]^+$, 238(9) $[M-C_6H_6NSO_2]^+$, 237(14) $[M-C_6H_7NSO_2]^+$, 168(40) $[M-C_{10}H_{12}NSO_3]^+$, 167(36) $[M-C_{10}H_{13}NSO_3]^+$, 141(42) $[M-C_{16}H_{17}N_2O]^+$, 77(100) $[M-C_{16}H_{17}N_2SO_3]^+$.

Anal. Calcd. for $C_{22}H_{22}N_2SO_3$: C, 67.00; H, 5.58; N, 7.11. Found: C, 66.92; H, 5.54; N, 7.18.

REFERENCES AND NOTES

[1] M. Amat, M. D. Coll, J. Bosch, E. Espinosa and E. Molins, *Tetrahedron* , **8**, 935 (1997).

[2] M. Amat, A. Linares, M. L. Salas, M. Alveres and J. Bosch, *J. Chem. Soc. Chem. Commun.*, 420 (1988).

[3] M. Amat, M Alvares, J. Bonjoch, N. Casamitjana, J. Gracia, R. Lavilla, X. Garcias and J. Bosch , *Tetrahedron Letters*, **31**, 3453 (1990).

[4] S. Patir, P. Rosenmund and P. H. Götz, *Heterocycles*, **43**, 15 (1996).

[5] S. Patir, *Liebigs Ann.*, 1561 (1995).

[6] P. Magnus, N. L. Sear, C. S. Kim and N. Vicker, *J. Org. Chem.*, **57**, 70 (1992).

[7] Y. Ergün, N. Bayraktar, S. Patir and G. Okay, *J. Heterocyclic Chem.*, **37**, 11 (2000).

[8] B. Robinson, *Chem. Rev.*, **63**, 373 (1963).

[9] H. Fritz, M. S. Jamarani, J. W. Bats and H. J. Teuber, *Liebigs Ann. Chem.*, 705 (1993).

[10] C. R. Hauser and D. S. Hoffenberg, *J. Org. Chem.*, **20**, 1448 (1955).

[11] Noller, *Org. Syntheses*, Coll. Vol. **II**, 586 (1943).