

**SYNTHESIS OF GABA-ANALOGOUS SPIROCYCLIC AMINO ACIDS, 4.
N-BENZYL-2-AZASPIRO[4.4]NONANE-6-CARBOXYLATES**

Gabriele Hollauf and Ernst Urban*

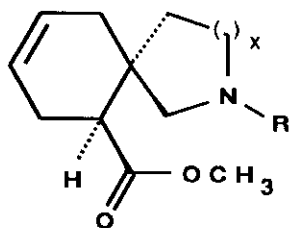
Institute of Pharmaceutical Chemistry, University of
Vienna, Währinger Straße 10, A-1090 Vienna, Austria

Abstract - Alkylation of 2-oxocyclopentanecarboxylate (4) with 1,2-dibromoethane and reaction with benzylamine gave 2-azaspiro[4.4]nonane-1,6-dione (7). After selective reduction of 7 at the lactam function, we obtained 2-azaspiro[4.4]nonan-6-one (9) which was treated with TosMIC/*tert*-BuOK to yield a mixture of diastereomeric nitriles (11a) and (11b). Hydrolysis followed by esterification and mpls separation led to diastereomerically pure esters (3a) and (3b) which represent novel analogs of GABA with restricted conformational flexibility.

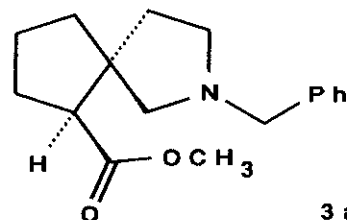
INTRODUCTION

4-Aminobutyric acid (GABA) is one of the most important inhibitory neurotransmitters in central nervous system.^{1,2} Extensive structure-activity studies on conformationally restricted analogues of GABA have revealed structural requirements, which are significant for agonists and antagonists acting at GABA-A or GABA-B receptors and for inhibitors of GABA uptake.³ Whereas steric demands for synthetic ligands of GABA receptor sites are rather high, a greater tolerance towards ring annelation of the GABA skeleton has been observed for compounds binding to the transport carrier of GABA.^{3,4} Thus restricted analogues of GABA, which have been created by incorporation of the GABA skeleton into carbocyclic or heterocyclic rings, are valuable targets for development of selective inhibitors of the GABA uptake system.

Scheme 1. GABA-analogous amino acids based on spirocyclic ring systems.



1,2



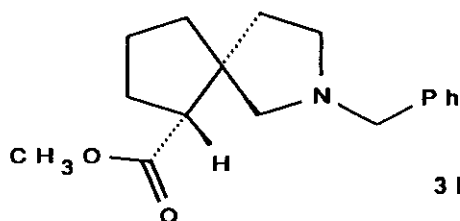
3 a

1 a, 2 a R = PhCH₂

1 b, 2 b R = Ph₂CH(CH₂)₂

1 a, 1 b x = 1

2 a, 2 b x = 2



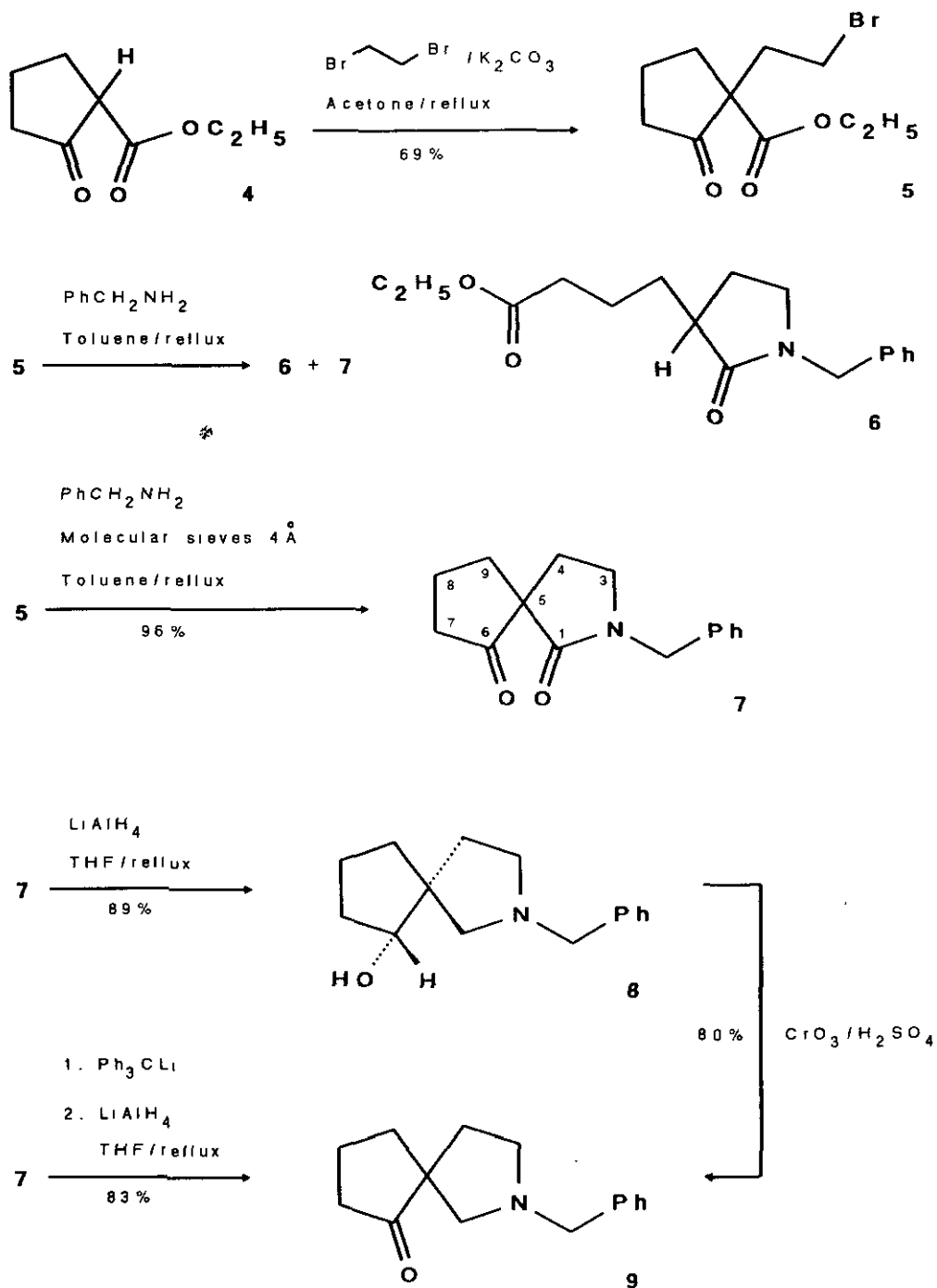
3 b

Our programme on development of selective GABA uptake inhibitors⁵ is concerned about spirocyclic amino acids which have been created by incorporation of the GABA skeleton into both a carbocyclic and a heterocyclic ring (Scheme 1). In a recent paper⁵ we presented syntheses of 2-azaspiro[4.5]decane (1a) and 2-azaspiro[5.5]undecane (2a) and prepared derivatives (1b) and (2b) by this method⁵ which turned out to be selective GABA uptake inhibitors. The matter of fact that substitution of a pyrrolidine ring (1b, IC₅₀ = 9.41 μM) for a piperidine ring (2b, IC₅₀ = 42.21 μM) increased the uptake inhibition potency persuaded us to synthesize the more restricted spirocyclic amino acids (3a) and (3b).

RESULTS and DISCUSSION

We started our synthesis from commercially available β-keto ester (4) which was alkylated by 1,2-dibromoethane (Scheme 2) following the procedure of T. Jaworski.⁶ Reaction of resulting bromoalkyl ester (5) with benzylamine yielded a mixture of pyrrolidone (6) and spirocyclic lactam (7) in the ratio of 1:1. Desired spirocyclic lactam (7) was the single product, if ethanol, which was eliminated during lactam formation, was removed from the reaction mixture by adsorption to molecular sieves.

Scheme 2. Preparation of spirocyclic ketone (9) from β -keto ester (4).



Treatment of β -keto lactam (7) with lithium aluminium hydride resulted in reduction of both the lactam and the ketone function to give spirocyclic amino alcohol (8) as a single product. Recently Fujii⁷ described reduction of a spirocyclic β -keto lactam homologous to 7 leading to an alcohol equal configured as 8.

First we considered diastereomerically pure alcohol (8) to be a valuable starting material for the synthesis of desired spirocyclic amino acids (3a and 3b) via their nitriles (11a and 11b) because both diastereomers should be selectively accessible carrying out substitution reaction either with retention or with inversion of configuration at C-6. But contrary to our expectations attempts failed to substitute a cyano function for the hydroxy group at C-6 of 8 by standard methods,^{8,9} obviously due to neopentyl structure of the alcohol (8). Therefore we oxidized 8 by Jones reagent to spirocyclic ketone (9) which we intended to convert to nitriles (11a and 11b) via hydrazones (10a or 10b). A more direct access to ketone (9) was achieved from spiro lactam (7) by enolization of the ketone function with triphenylmethyl lithium and by subsequent reduction of the non-enolizable lactam group with lithium aluminium hydride.

Reaction of ketone (9) with *p*-toluenesulfonylhydrazide (Scheme 3) gave the well crystallizing anti-hydrazone (10a)¹⁰ as a single product. Treatment of hydrazone (10a) with KCN in refluxing dichloromethane resulted in a complex mixture from which we isolated anti-hydrazone (10a, 18%), isomeric syn-hydrazone (10b, 19%)¹⁰ and desired nitriles (11a and 11b, 19%).¹¹ Finally reaction of ketone (9) with tosylmethyl isocyanide (TosMIC)¹⁴ turned out to be the method of choice for preparation of nitriles (11a and 11b). Best results were obtained using *tert*-BuOK in DMSO for deprotonation of TosMIC and carrying out reaction with ketone (9) at 45°C for 4 days to give a 1:1 mixture of diastereomeric nitriles (11a and 11b) in 86% yield. After chromatographic separation we isolated nitriles (11a, 39%) and (11b, 34%) as pure diastereomers.

Great shift differences of C-1 and C-4 in ¹³C nmr spectra of 11a and 11b (Table 1), which are caused by a typical gamma gauche effect¹⁵ of the vicinal cyano function either to C-1 in 11a or to C-4 in 11b, allowed structure assignment.

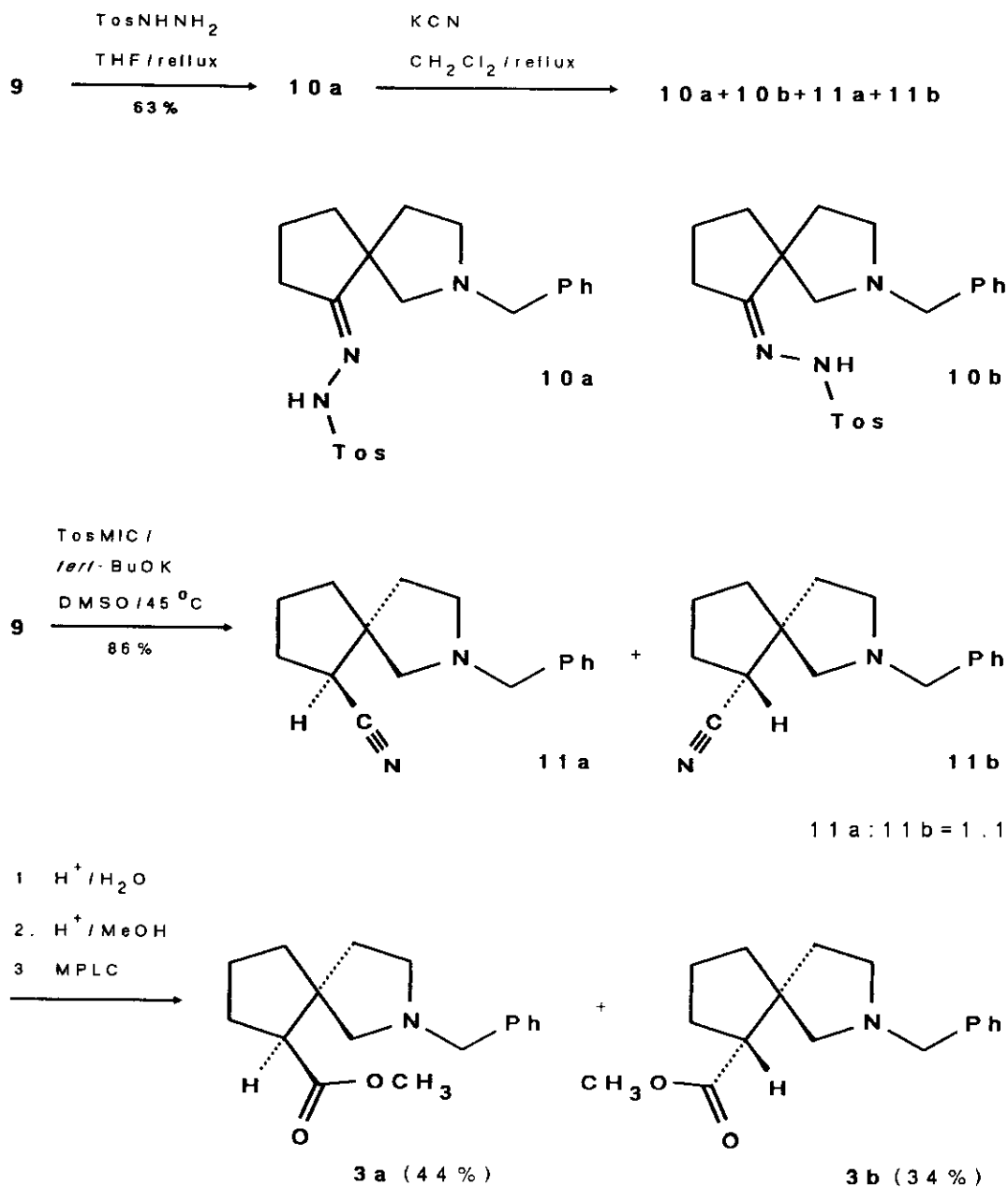
Scheme 3. Conversion of ketone (**9**) to amino esters (**3a**) and (**3b**).

Table 1. ^{13}C -Shifts (CDCl_3 , δ in ppm) of *N*-Benzyl-2-azaspiro[4.4]nonanes

	<u>3a</u>	<u>3b</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10a</u>	<u>10b</u>	<u>11a</u>	<u>11b</u>
C-1	61.70	65.47	172.95	60.80	62.33	64.27	60.98	62.09	64.44
C-3	53.31	53.85	43.92	52.74	53.99	53.82	53.88	53.31	53.35
C-4	37.23	32.94	29.09	35.34	36.89	39.78	41.14	36.66	34.11
C-5	52.96	52.92	58.20	51.12	55.12	52.95	49.78	52.28	52.33
C-6	53.44	52.37	217.12	81.40	221.53	170.77	165.78	39.42	39.15
C-7	27.56	27.80	37.57	32.68	38.31	27.55	34.18	29.12	29.17
C-8	22.27	22.37	19.59	20.22	19.44	21.40	22.09	21.84	22.17
C-9	40.07	40.10	33.91	34.45	35.33	37.19	36.05	38.21	38.00
Benzyl	60.34	60.25	46.61	59.96	59.81	60.10	59.33	59.95	59.80
C-1'	139.28	139.33	135.84	138.28	138.91	139.15	137.10	138.94	138.96
C-2', C-6'	128.61	128.46	128.43	128.45	128.46	128.56	129.17	128.39	128.25
C-3', C-5'	128.04	128.05	127.61	128.17	128.03	128.04	128.45	128.06	128.05
C-4'	126.69	126.68	127.28	126.90	126.70	126.74	127.51	126.73	126.69

Hydrolysis of diastereomerically pure nitrile (11a) in concentrated hydrochloric acid followed by acid catalysed esterification gave the methyl esters (3a) and (3b) in a ratio of 90:10. Attempts to avoid isomerisation at C-6 during conversion of 11a to 3a using more gently reaction conditions failed. Thus we started hydrolysis from a mixture of diastereomeric nitriles (11a) and (11b) receiving a mixture of esters (3a) and (3b) in a ratio of 1:1, which was separated by mplc to give esters (3a, 44%) and (3b, 34%) in a diastereomeric purity of >98% (hplc).

Structure assignment of 3a and 3b was determined by comparison of ^{13}C nmr data (Table 1), which revealed down field shifts of C-1 in 3a and of C-4 in 3b due to gamma gauche effect¹⁵ of vicinal carboxylic function. Further analytical data (^1H nmr, ir and ms) of 3a and 3b were completely in accordance with postulated structures.

We now want to prepare derivatives of 3a and 3b bearing a diarylalkyl substituent instead of the benzyl group at the nitrogen for pharmacological testing of GABA uptake inhibition.

ACKNOWLEDGEMENT

G. Hollauf thanks the "Bundesministerium für Wissenschaft und Forschung" for a scholarship.

EXPERIMENTAL

All melting points were determined on a KOFLEER melting point apparatus and are uncorrected. ^1H and ^{13}C nmr spectra were recorded on a BRUKER AC 80 or a VARIAN unity plus 300 spectrometer, using tetramethylsilane as internal standard. Infrared spectra were recorded on a PERKIN ELMER 298 spectrophotometer. Mass spectra were detected on a VARIAN MAT-111A spectrograph by L. Jirovetz. Mplc was performed with a PHARMACIA pump (P-500), a BÜCHI column (460x36 mm, Lichroprep Si 60, 15-25 μm), a PHARMACIA single path monitor (UV-1, 254 nm), and a PHARMACIA fraction collector (FRAC-200). The hplc system consisted of a Shimadzu pump (LC-10AD), a REODYNE injection valve (20 μl), a MERCK column (250x4 mm, Lichrospher Si 60, 5 μm), a SHIMADZU UV/vis detector (SPD-10A, 254 nm) and a HEWLETT PACKARD integrator (HP 3396A). Microanalyses were determined by J. Theiner (Institute of Physical Chemistry).

Conversion of nitriles (11a) and (11b) to amino esters (3a) and (3b):

A solution of nitriles (11a:11b = 1:1, 1.76 g, 7.32 mmol) in 37% HCl (60 ml) was refluxed for 16 h. Then HCl was distilled off in vacuo, the residue was dissolved in methanol (60 ml), *p*-toluenesulfonic acid (20 mg) was added and the mixture was refluxed once again for 16 h. After evaporation of the solvent, the residue was dissolved in dichloromethane, washed with 2 M NH_4OH , dried (Na_2SO_4) and the solvent was distilled off in vacuo to yield a mixture of 3a and 3b (1:1, 1.86 g). Mplc separation (silica gel, 211 g; hexane:EtOAc:2PrOH = 850:135:15; flow 500 ml/h; 3 runs) gave 3a (875 mg, 44%, colourless oil) and 3b (685 mg, 34%, colourless oil). Hplc analysis (silica gel, hexane:EtOAc:MeOH = 85:13:2, flow 1 ml/min) of 3a (R_t = 14.3 min) and 3b (R_t = 16.2 min) revealed a purity of $\geq 98\%$. For analytical purpose 3a and 3b were treated with HCl (1 M in ether) and recrystallized from 2-PrOH to give 3a.HCl and 3b.HCl.

(5R*,6R*)-Methyl N-benzyl-2-azaspiro[4.4]nonane-6-carboxylate (3a)

^1H Nmr (CDCl_3): δ 7.38 - 7.18 (m, 5H, aromatic-H), 3.63 (s, 3H, OCH_3), 3.60 (d, $J = 13.3$ Hz, 1H, benzyl-H), 3.54 (d, $J = 13.3$ Hz, 1H, benzyl-H), 2.64 - 2.51 (m, 3H, H-3, H-6), 2.56 (d, $J = 9.5$ Hz, 1H, H-1), 2.28 (d, $J = 9.5$ Hz, 1H, H-1), 2.00 (ddd, $J = 12.7, 8.1$ and 6.3 Hz, 1H, H-4), 1.95 - 1.82 (m, 3H), 1.77 (ddd, $J = 12.7, 7.8$ and 6.1 Hz, 1H, H-4), 1.72 - 1.61 (m, 3H). ^{13}C Nmr (CDCl_3): δ 175.20 (COO), 51.19 (OCH_3), for further signals see Table 1. Ms: m/z 273 (M^+), 258 (M^+-15), 182 (M^+-91), 91 (PhCH_2^+). 3a.HCl: (colourless crystals, mp 123°C). Ir (KBr) 1730 cm^{-1} (ester). Anal. Calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_2\cdot\text{HCl}$: C, 65.90; H, 7.81; N, 4.52. Found C, 65.82; H, 7.78; N, 4.26.

(5R*,6S*)-Methyl N-benzyl-2-azaspiro[4.4]nonane-6-carboxylate (3b)

^1H Nmr (CDCl_3): δ 7.34 - 7.18 (m, 5H, aromatic-H), 3.66 (s, 3H, OCH_3), 3.59 (s, 2H, benzyl-H), 2.66 - 2.48 (m, 3H, H-3, H-6), 2.56 (d, $J = 9.0$ Hz, 1H, H-1), 2.43 (d, $J = 9.0$ Hz, 1H, H-1), 2.01 - 1.50 (m, 8H). ^{13}C Nmr (CDCl_3): δ 175.50 (COO), 51.11 (OCH_3), for further signals see Table 1. Ms: m/z 273 (M^+), 258 (M^+-15), 182 (M^+-91), 91 (PhCH_2^+). 3b.HCl: (colourless crystals, mp 127°C). Ir (KBr) 1725 cm^{-1} (ester). Anal. Calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_2\cdot\text{HCl}$: C, 65.90; H, 7.81; N, 4.52. Found C, 65.60; H, 7.58; N, 4.30.

Reaction of 5 with benzylamine:

A solution of 5⁶ (3.39 g, 12.9 mmol) and benzylamine (4.15 g, 38.7 mmol) in toluene (50 ml) was refluxed for 16 h. Then 2 M HCl (30 ml) was added and the mixture was stirred at 20°C for 1 h. The organic layer was separated, washed with 2 M HCl, dried (Na_2SO_4) and the solvent was evaporated to give a 1:1 mixture of 6 and 7 (3.3 g). Separation by flash chromatography (silica gel, hexane:EtOAc = 1:1) gave 7 (523 mg, 17%, colourless oil, $R_f = 0.4$) and 6 (654 mg, 18%, colourless oil, $R_f = 0.27$).

Ethyl 4-(N-benzyl-2-oxopyrrolidin-3-yl)butanoate (6)

^1H Nmr (CDCl_3): δ 7.40 - 7.20 (m, 5H, aromatic-H), 4.94 (d, $J = 14.7$ Hz, 1H, benzyl-H), 4.35 (d, $J = 14.7$ Hz, 1H, benzyl-H), 4.13 (q, $J = 7.5$ Hz, 2H, OCH_2), 3.90 - 3.14 (m, 2H, H-3'), 2.61 (t, $J = 5.9$ Hz, 2H, H-2), 2.50

- 1.55 (m, 7H), 1.26 (t, $J = 7.5$ Hz, 3H, CH_3). ^{13}C Nmr (CDCl_3): δ 175.64 (C-1'), 174.08 (C-1), 137.24 (C-1"), 128.35 (C-2", C-6"), 128.04 (C-3", C-5"), 127.21 (C-4"), 60.34 (OCH_2), 47.39 (benzyl-C), 44.47 (C-5'), 41.88 (C-3'), 33.81 (C-2), 31.16 (C-4'), 29.16 (C-4), 27.22 (C-3), 13.97 (CH_3). Ms: m/z 289 (M^+), 261 ($\text{M}^+ - 28$), 91 (PhCH_2^+). Anal. Calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_3$: C, 70.55; H, 8.07; N, 4.84. Found C, 70.29; H, 8.03; N, 4.86.

N-Benzyl-2-azaspiro[4.4]nonane-1,6-dione (7)

A solution of 5 (16.4 g, 62.3 mmol) and benzylamine (20.0 g, 187 mmol) in toluene (200 ml) was refluxed in a Soxhlet extractor filled with molecular sieves (4 Å) for 16 h. Then 2 M HCl (150 ml) was added and the mixture was stirred at 20°C for 1 h. The organic layer was separated, washed with 2 M HCl, dried (Na_2SO_4) and the solvent was evaporated to give 7 (14.5 g, 96%, yellow oil). For analytical purpose crude 7 (1.45 g) was purified by flash chromatography (silica gel, hexane:EtOAc = 1:1) to yield pure 7 (980 mg, 65%, colourless oil). ^1H Nmr (CDCl_3): δ 7.36 - 7.22 (m, 5H, aromatic-H), 4.51 (d, $J = 15.0$ Hz, 1H, benzyl-H), 4.46 (d, $J = 15.0$ Hz, 1H, benzyl-H), 3.44 (dt, $J = 9.0$ and 7.0 Hz, 1H, H-3), 3.17 (dt, $J = 4.0$ and 9.0 Hz, 1H, H-3), 2.59 (m, 1H), 2.47 (m, 1H), 2.38 - 2.27 (m, 3H), 1.98 - 1.87 (m, 2H), 1.83 (ddd, $J = 13.0$, 9.0 and 7.0 Hz, 1H, H-4). ^{13}C Nmr (CDCl_3): see Table 1. Ir (KBr) 1740 cm^{-1} (ketone), 1685 cm^{-1} (lactam). Ms: m/z 243 (M^+), 91 (PhCH_2^+). Anal. Calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_2$: C, 74.05; H, 7.04; N, 5.76. Found C, 73.75; H, 6.91; N, 6.01.

(5*R**,6*R**)-*N*-Benzyl-6-hydroxy-2-azaspiro[4.4]nonanone (8)

In an argon atmosphere 7 (6.8 g, 28 mmol) dissolved in THF (80 ml) was cooled to 0°C and LiAlH_4 (84 ml, 1 M in THF, 84 mmol) was added. After the reaction mixture was refluxed for 2 h, water (6.5 ml) was added dropwise and stirring was continued for 16 h. Then the precipitate was filtered off and washed with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and the solvent removed in vacuo to give 8 (5.8 g, 89%, colourless oil). ^1H Nmr (CDCl_3): δ 7.34 - 7.22 (m, 5H, aromatic-H), 3.80 (t, $J = 7.4$ Hz, 1H, H-6), 3.65 (d, $J = 13.0$ Hz, 1H, benzyl-H), 3.56 (d, $J = 13.0$ Hz, 1H, benzyl-H), 3.08 (d, $J = 9.3$ Hz, 1H, H-1), 2.97 (ddd, $J = 9.1$, 7.2 and 5.4 Hz, 1H, H-3), 2.28 (dt, $J = 7.9$ and 9.1 Hz, 1H, H-3), 2.03 (d, $J =$

9.3 Hz, 1H, H-1), 2.03 (m, 1H), 1.90 - 1.77 (m, 2H), 1.71 - 1.46 (m, 6H). ^{13}C Nmr (CDCl_3): see Table 1. Ir (KBr) 3420 cm^{-1} (OH). Ms: m/z 231 (M^+), 140 (M^+-91), 91 (PhCH_2^+). Anal. Calcd for $\text{C}_{15}\text{H}_{21}\text{NO}$: C, 77.87; H, 9.17; N, 6.05. Found C, 77.62; H, 9.31; N, 5.98.

N-Benzyl-2-azaspiro[4.4]nonane-6-one (9)

Method A: A solution of **8** (3.7 g, 16 mmol) in acetone (100 ml) was cooled to 0°C and treated with concentrated H_2SO_4 (1.6 g, 16 mmol). Jones reagent which was prepared from concentrated H_2SO_4 (3.7 g, 38 mmol), CrO_3 (2.5 g, 25 mmol) and H_2O (7.2 ml) was added dropwise, the reaction mixture was allowed to warm up to 20°C and stirring was continued for 4 h. Then 2-PrOH (16 ml) was added and acetone was distilled off at reduced pressure. After basification (pH = 10) with 6 M NaOH the precipitated slurry was filtered off, washed with ethyl acetate and the aqueous filtrate was extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and the solvent evaporated to give **9** (2.92 g, 80%, yellow oil).

Method B: In an argon atmosphere a solution of triphenylmethane (7.48 g, 30.6 mmol) in THF (100 ml) was reacted with *n*-BuLi (17.4 ml, 1.6 M in hexane, 27.8 mmol) at 0°C and stirring continued for 30 min. Then **7** (4.53 g, 18.6 mmol) dissolved in THF (50 ml) was added and stirring was continued for 30 min at 0°C . After addition of LiAlH_4 (18.6 ml, 1 M in THF, 18.6 mmol) at 0°C the mixture was refluxed for 2 h. Then H_2O (1.34 ml, 74.4 mmol) was added and the mixture was stirred for 1 h at 20°C . The resulting precipitate was filtered off and washed with ethyl acetate. The combined organic layers were concentrated in vacuo, diluted with ether and extracted with 0.1 M HCl. Evaporation of the organic layer allowed recycling of triphenylmethane (7.41 g, 99%). The aqueous layer was basified with 2 M NH_4OH and finally extracted with dichloromethane. The dichloromethane extracts were dried (Na_2SO_4) and the solvent removed in vacuo to give **9** (3.54 g, 83%, yellow oil). For analytical purpose crude **9** (440 mg) was purified by flash chromatography (silica gel, hexane: Et_3N = 95:5) to yield pure **9** (270 mg, 51%, colourless oil). ^1H Nmr (CDCl_3): δ 7.36 - 7.21 (m, 5H, aromatic-H), 3.65 (d, J = 12.8 Hz, 1H, benzyl-H), 3.61 (d, J = 12.8 Hz, 1H, benzyl-H), 2.82 (ddd, J = 8.9, 7.4 and 4.4 Hz, 1H, H-3), 2.56 (dt, J = 8.9 and 7.4 Hz, 1H, H-3), 2.55 (d, J = 9.8 Hz, 1H, H-1), 2.52 (d, J =

9.8 Hz, 1H, H-1), 2.32 - 2.10 (m, 2H), 2.26 (dt, $J = 19.2$ and 7.9 Hz, 1H, H-7), 2.06 (ddd, $J = 12.3$, 7.4 and 4.4 Hz, 1H, H-4), 1.98 (dt, $J = 22.5$ and 6.7 Hz, 1H, H-9), 1.92 - 1.76 (m, 2H), 1.66 (dt, $J = 12.3$ and 7.4 Hz, 1H, H-4). ^{13}C Nmr (CDCl_3): see Table 1. Ir (KBr) 1730 cm^{-1} (ketone). Ms: m/z 229 (M^+), 138 (M^+-91), 91 (PhCH_2^+). Anal. Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}$: C, 78.56; H, 8.35; N, 6.11. Found C, 78.33; H, 8.31; N, 5.75.

(E)-N-Benzyl-2-azaspiro[4.4]nonan-6-one tosylhydrazone (10a)

A solution of 9 (1.147 g, 5 mmol) and *p*-toluenesulfonylhydrazide (931 mg, 5 mmol) in THF (50 ml) was refluxed in a Soxhlet extractor filled with molecular sieves (4 Å) for 2 h. Then the solvent was evaporated and the residue was crystallized from ether/MeOH to give 10a (1.25 g, 63%, colourless crystals, mp 134°C). ^1H Nmr (CDCl_3): δ 7.86 (d, $J = 7.9$ Hz, 2H, $\text{SO}_2\text{Ar-H}$), 7.34 - 7.21 (m, 7H, aromatic-H), 3.67 (d, $J = 12.8$ Hz, 1H, benzyl-H), 3.58 (d, $J = 12.8$ Hz, 1H, benzyl-H), 2.85 (dt, $J = 3.9$ and 8.1 Hz, 1H, H-3), 2.59 (d, $J = 9.4$ Hz, 1H, H-1), 2.54 (q, $J = 8.1$, 1H, H-3), 2.44 (m, 1H), 2.43 (s, 3H, CH_3), 2.23 - 2.12 (m, 2H), 1.98 (ddd, $J = 12.3$, 7.9 and 3.9 Hz, 1H, H-4), 1.85 - 1.62 (m, 6H). ^{13}C Nmr (CDCl_3): 143.69 (C-1"), 135.42 (C-4"), 129.27 (C-3", C-5"), 128.04 (C-2", C-6"), 21.50 (CH_3), for further signals see Table 1. Anal. Calcd for $\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_2\text{S}$: C, 66.47; H, 6.85; N, 10.57. Found C, 66.24; H, 6.60; N, 10.71.

Reaction of 10a with HCN:

KCN (469 mg, 7.2 mmol) was added to a solution of 10a (954 mg, 2.4 mmol) in dichloromethane (20 ml) and the mixture was refluxed for 16 h. The precipitated crystals were removed by filtration and the filtrate was washed with 2 M NH_4OH . The organic layer was dried (Na_2SO_4) and the solvent distilled off in vacuo. Separation by flash chromatography (silica gel, hexane:EtOAc:Et₃N = 7:2:1) gave a mixture of 11a and 11b (109 mg, 19%, colourless oil, $R_f = 0.46$) and 10a (185 mg, 19%, colourless crystals, mp 134°C , $R_f = 0.24$). Further elution (hexane:EtOAc:Et₃N = 5:4:1) yielded 10b (171 mg, 18%, colourless oil, $R_f = 0.34$).

(Z) N-Benzyl-2-azaspiro[4.4]nonan-6-one tosylhydrazone (10b)

^1H Nmr (CDCl_3): δ 7.66 (d, $J = 8.0$ Hz, 2H, $\text{SO}_2\text{Ar-H}$), 7.55 - 7.10 (m, 7H, aromatic-H), 3.62 (s, 2H, benzyl-H), 3.20 (m, 1H, H-3), 3.01 (d, $J = 9.6$ Hz, 1H, H-1), 2.35 (s, 3H, CH_3), 2.50 - 1.2 (m, 11H). ^{13}C Nmr (CDCl_3): 142.69 (C-1"), 136.75 (C-4"), 129.41 (C-3", C-5"), 127.14 (C-2", C-6"), 21.38 (CH_3), for further signals see Table 1. Anal. Calcd for $\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_2\text{S}$: C, 66.47; H, 6.85; N, 10.57. Found C, 66.28; H, 6.77; N, 10.67.

Conversion of ketone (9) to nitriles (11a) and (11b):

In an argon atmosphere a solution of tosylmethyl isocyanide (4.6 g, 23.6 mmol) in dry DMSO (40 ml) was cooled to 0°C , reacted with tert-BuOK (8.3 g, 74 mmol) and stirred at 20°C for 10 min. Then dry methanol (3 ml) and a solution of **9** (2.29 g, 10 mmol) in dry DMSO (5 ml) were added and the resulting mixture was heated to 45°C for 4 d. After addition of a saturated solution of NaHCO_3 (50 ml) the mixture was extracted with ether. The combined organic layers were washed with a saturated solution of NaHCO_3 , dried (Na_2SO_4) and the solvent was removed in vacuo to yield a 1:1 mixture of **11a** and **11b** (2.06 g, 86%, yellow oil). For analytical purpose the mixture of diastereomers (200 mg) was separated by flash chromatography (silica gel, hexane: $\text{Et}_3\text{N} = 95:5$) to yield pure **11b** (90 mg, 39%, colourless oil, $R_f = 0.32$) and **11a** (79 mg, 34%, colourless oil, $R_f = 0.29$). Reaction of **11a** and **11b** with HCl (1 M in ether) and recrystallization from 2-PrOH gave **11a.HCl** and **11b.HCl**.

(5R*,6R*)-N-Benzyl-2-azaspiro[4.4]nonane-6-carbonitrile (11a)

^1H Nmr (CDCl_3): δ 7.37 - 7.20 (m, 5H, aromatic-H), 3.68 (d, $J = 12.9$ Hz, 1H, benzyl-H), 3.60 (d, $J = 12.9$ Hz, 1H, benzyl-H), 2.77 (d, $J = 9.5$ Hz, 1H, H-1), 2.70 - 2.61 (m, 3H, H-3, H-6), 2.50 (d, $J = 9.5$ Hz, 1H, H-1), 2.06 (ddd, $J = 8.8, 7.8$ and 5.1 Hz, 1H, H-4), 1.95 - 1.85 (m, 2H), 1.82 - 1.72 (m, 3H), 1.69 - 1.56 (m, 2H). ^{13}C Nmr (CDCl_3): δ 121.41 ($\text{C}\equiv\text{N}$), for further signals see Table 1. Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{N}_2$: C, 79.96; H, 8.39; N, 11.66. Found C, 79.81; H, 8.61; N, 11.38. **11a.HCl**: (colourless crystals, mp 182°C). Ir (KBr) 2240 cm^{-1} ($\text{C}\equiv\text{N}$).

(5R*,6S*)-N-Benzyl-2-azaspiro[4.4]nonane-6-carbonitrile (11b)

^1H Nmr (CDCl_3): δ 7.37 - 7.16 (m, 5H, aromatic-H), 3.61 (s, 2H, benzyl-H), 2.75 (dt, $J = 6.2$ and 8.8 Hz, 1H, H-3), 2.69 (dd, $J = 8.1$ and 6.6 Hz, 1H, H-6), 2.65 (dt, $J = 5.6$ and 8.8 Hz, 1H, H-3), 2.46 (d, $J = 9.3$ Hz, 1H, H-1), 2.40 (d, $J = 9.3$ Hz, 1H, H-1), 2.15 (ddd, $J = 12.7$, 8.8 and 5.6 Hz, 1H, H-4), 2.08 - 1.93 (m, 2H), 1.86 - 1.73 (m, 3H), 1.73 - 1.60 (m, 2H). ^{13}C Nmr (CDCl_3): δ 121.65 (C \equiv N), for further signals see Table 1. Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{N}_2$: C, 79.96; H, 8.39; N, 11.66. Found C, 79.66; H, 8.45; N, 11.43. 11b.HCl: (colourless crystals, mp 186 - 187°C). Ir (KBr) 2240 cm^{-1} (C \equiv N).

REFERENCES

1. E. Roberts, T. N. Chase, and D. B. Tower, "GABA in Nervous System Function." Kroc Foundation Series, Vol. 5, Raven Press, New York, 1976.
2. R. D. Allan and G. A. R. Johnston, Med. Res. Rev., 1983, 3, 91.
3. P. Krosggaard-Larsen, P. Lenicque, and P. Jacobsen, "GABA ergic Drugs: Configurational and Conformational Aspects." CRC Handbook of Stereoisomers: Drugs in Psychopharmacology; ed. by D. F. Smith, CRC Press: Boca Raton, 1984, pp. 369 - 398.
4. L. Nielsen, L. Brehm, and P. Krosggaard-Larsen, J. Med. Chem., 1990, 33, 71.
5. C. Dostal, S. Lauritz, and E. Urban, Heterocycles, 1992, 34, 135.
6. K. Jarowicki and T. Jaworski, Monatsh. Chem., 1984, 115, 605.
7. M. Fujii, K. Kawaguchi, K. Nakamura, and A. Ohno, Chem. Lett., 1992, 1493.
8. R. Davis and K. G. Untch, J. Org. Chem., 1981, 46, 2985.
9. A. Mizuno, Y. Hamada, and T. Shioiri, Synthesis, 1980, 1007.
10. Stereochemistry of hydrazones (10a and 10b) was established due to typical shifts of C-5 and C-7 in ^{13}C nmr spectra (Table 1) in accordance to C. A. Bunnell and P. L. Fuchs, J. Org. Chem., 1977, 42, 2614.
11. Phase-transfer catalysed addition of HCN^{12} to 10a followed by thermal decomposition 13 gave exclusively hydrazones (10a) and (10b) instead of nitriles (11a) and (11b).
12. T. Chiba and M. Okimoto, Synthesis, 1990, 209.

13. S. Cacci, L. Caglioti, and G. Paolucci, Chem. Ind., **1972**, 213.
14. O. H. Oldenziel, D. van Leusen, and A. M. van Leusen, J. Org. Chem., **1977**, **42**, 3114.
15. E. Breitmaier and W. Voelter, "Carbon-13 NMR Spectroscopy, High Resolution Methods and Applications in Organic Chemistry and Biochemistry" VCH Verlagsgesellschaft, Weinheim, 1987, pp. 115-116.

Received, 20th June, 1994