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An Improved Synthesis and Resolution of Potentially Neuroleptic Rigid Spiro Amines

B. CARNMALM,[a] L. JOHANSSON,[a] S. RÄMSBY [a] and N. E. STJERNSTRÖM [b]

[a] Research and Development Laboratories, Astra Läkemedel AB, S-15185 Södertälje, Sweden and [b] Astra Pharmaceuticals AB, S-15185 Södertälje, Sweden

Details of the synthesis of the rigid spiro amines 3-chloro-*N*,*N*-dimethylspiro[5*H*-dibenzo[*a*,*d*]-cycloheptene-5,1′-cyclohex-2′-en]-4′-amine (*1*) and 3-chloro-10,11-dihydro-*N*,*N*-dimethylspiro-[5*H*-dibenzo[*a*,*d*]cycloheptene-5,1′-cyclohex-2′-en]-4-amine (*2*) are reported. Separation of the diastereomers and their resolution are described. All possible enantiomers are characterized.

The synthesis and resolution of novel types of tetracyclic spiro amines, *1* and *2*, with central dopamine receptor-blocking properties have recently been reported.[1,2] It was shown that the blocking activity resides in one of the enantiomers of *2*, thus demonstrating a high stereoselectivity.[2] The synthesis of the spiro amines is outlined in Scheme 1.

We now report improvements of the original synthetic route [1] and describe details of the isomer separation.[2] The carcinogenicity of chloromethyl ethers has obliged us to develop other synthetic methods for the aldehydes *5* and *6*.

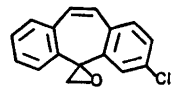

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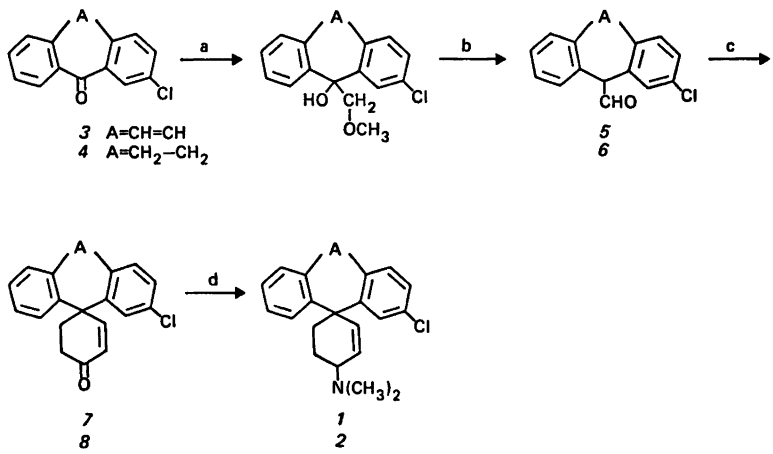
Fig. 1.

Dimethyl sulfoxoniummethylide [3] was reacted with the ketone *3* to give the epoxide *9*, in analogy with a procedure for preparing the corresponding non-chlorinated compound.[4] The epoxide was rearranged to the aldehyde *5* in high yield.



3 A=CH=CH
4 A=CH_2–CH_2
5
6
7
8
1
2

Scheme 1. Reagents: a, CH_3OCH_2Cl, Mg; b, H_3O^+; c, $CH_2=CHCOCH_3$, OH^-; d, $HCON(CH_3)_2$.

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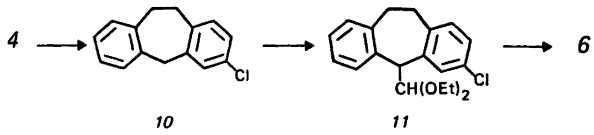
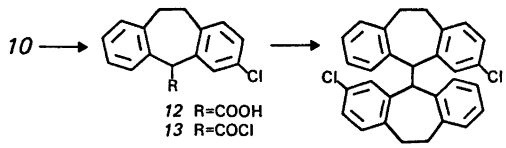


Scheme 2.

The synthesis of the aldehyde *6* was accomplished by reacting the anion of *10* with diethyl phenyl orthoformate [5] to give the acetal *11*, which was hydrolyzed to the desired aldehyde *6*. An attempted Rosenmund reaction with the acyl chloride *13* gave only compound *14*. The structure of *14* was established by a coupling reaction between 3,5-dichloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene [6] and the anion of *10*, and also by an X-ray crystallographic investigation.[7]



Scheme 3.

The spiro annelation reaction with methyl vinyl ketone to the tetracyclic ketones *7* and *8*, was performed essentially as described previously.[1] The yield was somewhat improved by adding the basic catalyst as slowly as possible. The crude product could conveniently be used directly in the Leuckart reaction. The final separation of the dimethylamines *1* and *2*, respectively, was simple and convenient for large scale preparations although chromatography had to be used.

The separation of the diastereomers of the amine *1* has been carried out in the following way. The oxalate of *1* was crystallized from ethanol to give the pure isomer *1a*. The remaining mixture of diastereomers *1a* and *1b* was converted to the hydrochlorides which were recrystallized from ethanol to give pure *1b*. The progress of the separations was followed by HPLC. The resolution of *1a* and *1b* into their enantiomers was achieved by fractional crystallization of the salts with optically active mandelic acid and dibenzoyltartaric acid, respectively.

The separation of the diastereomers of the amine *2*, was performed in a similar way, making use of the difference in the solubility of the hydrochlorides of the isomers of *2* in hot acetone, which resulted in a partial separation. *2a* was isolated as the hydrochloride from acetonitrile and *2b* as the oxalate from ethanol. NMR spectroscopy was used to follow the separation.

When trying to develop an ion pair HPLC method to separate *2a* and *2b*, it was found that the phosphate of *2b* in contrast to that of *2a* is almost insoluble in pentanol. This finding was utilized in a more convenient large scale separation of the isomers.

The resolution of *2a* and *2b* into the enantiomers was achieved by fractional crystallization of the salts with optically active mandelic acid and di-*p*-toluoyltartaric acid, respectively. In order to elucidate the detailed structures including absolute configuration, X-ray diffraction work is in progress.

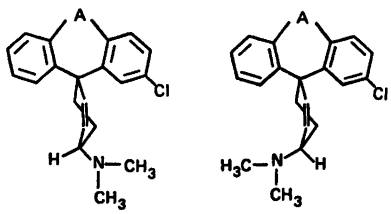


Fig. 2. The diastereomers *1a*, *1b* and *2a*, *2b*. The presently available data do not permit the individual diastereomers to be identified.

EXPERIMENTAL

Melting points are uncorrected. The structures of the new compounds were confirmed by IR (Perkin Elmer 720), ^{1}H NMR (Varian T60), ^{13}C NMR (Varian CFT-20) and MS (LKB 9000). GLC was performed using a Perkin Elmer 3920 chromatograph with a 3 % OV-17 on Gas Chrome Q column and HPLC using a Lichrosorb Si-60 10 μm column with isooctane + EtOH + conc. NH_3, 95 + 5 + 0.1, as eluent. Optical rotations were measured with a Perkin Elmer 141 polarimeter. Elemental analyses were

performed at the laboratories of Dr. Alfred Bernhardt, Elbach über Engelskirchen, West Germany and at the Department of Analytical Chemistry, Chemical Center, University of Lund, Sweden.

3-Chloro-N,N-*dimethylspiro*[*5*H-*dibenzo*[a,d]-*cycloheptene-5,1'-cyclohex-2'-en*]-*4'-amine (1).* Crude aldehyde *5*, (30 g) *ca.* 90 % purity (GLC) from 30 g (0.125 mol) ketone *3*, was dissolved in 200 ml of dry THF and freshly distilled methyl vinyl ketone (9 g, 0.13 mol) was added in one portion. To the solution, 4 ml of 3 M KOH in EtOH was added under nitrogen at 10 °C during 90 min with the help of a syringe pump. Stirring was continued for a further 5 h while the temperature was allowed to reach room temperature. The alkaline solution was neutralized with a few drops of concentrated HCl and the solvent was removed by distillation. The Leuckart reaction was performed as described previously,[1] but using the crude spiro ketone, giving 30 g of amine *1*. Column chromatography on 1.5 kg of basic Al_2O_3, activity 3, with gradient elution 10 – 30 % $(iPr)_2O$ in hexane gave 11 g of the amine *1*, yield 28 % from *5*. HPLC showed that the mixture contained equal amounts of the diastereomers.

Separation of the isomers 1a *and* 1b. Co pound *1* (20 g) was converted to the oxalate, which was recrystallized once from CH_3CN + EtOH 90 + 10 and twice from abs. EtOH. The *1a* oxalate (6 g) was obtained in 93 % purity (HPLC). A small sample was converted into the hydrochloride and recrystallized from EtOH to an isomeric purity > 99 % (HPLC), m.p. 254 – 256 °C. Anal. ($C_{22}H_{23}Cl_2N$) C, H, Cl, N.

A mixture of *1a* and *1b* (10 g) from the mother liquor was converted into the hydrochloride and recrystallized twice from EtOH. The isomer *1b* (6 g) was obtained with a 94 % purity (HPLC). A small sample was further purified by recrystallization from EtOH to > 99 % (HPLC), m.p. 268 – 270 °C. Anal. ($C_{22}H_{23}Cl_2N$) C, H, Cl, N.

3-Chloro-10,11-dihydro-N,N-*dimethylspiro*[*5*H-*dibenzo*[a,d]-*cycloheptene-5,1'-cyclohex-2'en*]-*4-amine (2).* The title compound was prepared essentially as described previously [1] from the aldehyde *6* (200 g, 0.78 mol) with the following modifications. The addition of base was made slowly overnight by means of a syringe pump. After neutralization with concentrated HCl the solvent was evaporated giving 250 g of the crude spiroketone, which was used directly in the Leuckart reaction performed as described previously.[1] From the basic material the amine *2* was isolated by chromatography on a basic alumina column (Merck 3 kg, activity grade 3) and gradient elution with 10 – 30 % isopropyl ether in hexane. Yield 90 g (28 % from the aldehyde) containing about 55 % of *2a* and 45 % of *2b* (HPLC).

Separation of the isomers 2a *and* 2b. *Method 1.* The spiroamine.HCl (*2*) (37 g, 0.1 mol) was extracted twice with 400 ml portions of hot acetone. The remaining crystalline mass (27.5 g) was recrystallized from MeCN yielding 22 g of *2a*. HCl, m.p. 257 – 259 °C. Anal. ($C_{22}H_{25}Cl_2N$) C, H, Cl, N.

From the combined extracts and mother liquors the other isomer, *2b*, was isolated as the oxalate. Recrystallization from EtOH gave 9.5 g, m.p. 226 – 228 °C.

Method 2. The amine (15 g) containing *2a* and *2b* was dissolved in 300 ml of pentanol. A 10 % aqueous solution of H_3PO_4 was added in about 100 % excess. After stirring for 3 h the precipitate was filtered off giving 8.0 g of the phosphate of *2b*. The base was found after HPLC analysis to contain 95 % of *2b*. Recrystallization of the hydrochloride from acetone gave the pure isomer *2b* (4.2 g), m.p. 226 – 228 °C. Anal. ($C_{22}H_{25}Cl_2N.H_2O$) C, H, Cl, N, O.

The mother liquor obtained after the precipitation with H_3PO_4 contained 11.5 g of *2a* in 90 % purity. Recrystallization of the hydrochloride from MeCN afforded pure *2a*.

Resolution of the racemates 1a, 1b, 2a *and* 2b. Experimental conditions for the resolutions and physical constants of the enantiomers are summarized in Table 1. The resolving acid in dry ether was added to a solution of the amine in dry ether in the molar proportion 1.1:1. The precipitated salt was recrystallized from the indicated solvent until it showed constant optical rotation. From the combined mother liquors the other enantiomer was isolated similarly. For pharmacological testing, other salts of the optically active amines were prepared as shown in the table. Optical rotations were measured in 0.5 % w/v solutions at room temperature.

*3-Chloro-5*H-*dibenzo*-[a,d]*cycloheptene-5-carboxaldehyde (5).* *p*-Toluenesulfonic acid (70 mg, 0.4 mmol) was added to the benzene solution of crude *9*, from 6 g of the ketone *3*, and heated under reflux for 20 min. After cooling, the solution was neutralized by adding an $NaHCO_3$ solution. Drying (Na_2SO_4) and evaporation gave 6 g of an oil, which crystallized on standing. Recrystallization from Et_2O gave 4 g of aldehyde, which had m.p. 130 – 132 °C (Lit.[1] 133 – 134 °C).

*3-Chloro-10,11-dihydro-5*H-*dibenzo*[a,d]*cycloheptene-5-carboxaldehyde (6).* The acetal *11* (80 g, 0.24 mol) was dissolved in 400 ml of dioxane and treated with 30 ml of aqueous 2 M HBF_4 at 90 °C for 2.5 min. The reaction was stopped by adding $NaHCO_3$. After filtration and drying ($MgSO_4$) the solvent was evaporated giving an oil, which crystallized. Recrystallization from MeCN gave 62 g (78 %) of compound *6* m.p. 147 – 148 °C. (Lit.[1] 144 – 146 °C).

*3-Chloro-5-methylene-5*H-*dibenzo*[a,d]*cycloheptene-5,12-oxide (9).* The synthesis of the epoxide was performed essentially as described [4] for the preparation of 5-methylene-5*H*-dibenzo-[*a,d*]-cycloheptene-5,12-oxide using 10 g (0.045 mol) of freshly recrystallized $(CH_3)_3SO^+I^-$,[3] 100 ml of dry DMSO, 24 ml 1.7 M (0.040 mol)

Table 1. The enantiomers of spiro amines *1* and *2*.

Amine	Salt	$[\alpha]_D^{25}$/deg.	Solvent for recryst.	No. of recryst.	M.p./°C [e]	Elemental analyses [e]
(+)-*1a*	L(+)-MA [a]	+151	iPrOH	4		
(+)-*1a*	Free base	+218	iPr_2O	1	125–126	C, H, Cl, N
(−)-*1a*	D(−)-MA	−152	iPrOH	4		
(−)-*1a*	Free base	−220	iPr_2O	1	125–126	C, H, Cl, N
(+)-*1b*	D(+)-BTA [b]	+ 55	EtOH	3		
(+)-*1b*	HCl	+ 27	EtOH	1	260–261	C, H, Cl, N
(−)-*1b*	L(−)-BTA	− 55	EtOH	3		
(−)-*1b*	HCl	− 27	EtOH	1	260–261	C, H, Cl, N
(+)-*2a*	L(+)-MA	+184	iPrOH	2		
(+)-*2a*	HCl	+150 [c]	iPrOH	1	259–260	C, H, Cl, N
(−)-*2a*	D(−)-MA	−201	iPrOH	2		
(−)-*2a*	HCl	−149 [c]	iPrOH	1	257–259	C, H, Cl, N
(+)-*2b*	D(+)-TTA [d]	+211	EtOH	3		
(+)-*2b*	Maleate	+204	EtOH	1	187–188	C, H, Cl, N
(−)-*2b*	L(−)-TTA	−208	EtOH	3		
(−)-*2b*	Maleate	−206	EtOH	1	187–188	C, H, Cl, N

[a] MA = Mandelic acid, [b] BTA = Dibenzoyltartaric acid, [c] Measured in EtOH; all other rotations were measured in $CHCl_3$. [d] TTA = Di-*p*-toluoyltartaric acid. [e] Amine hydrochloride.

of BuLi and 6 g (0.025 mol) of ketone *3*. After work up, the benzene solution was evaporated to a volume of about 100 ml. This solution was used directly in the rearrangement to the aldehyde *5*. A small sample was further purified by chromatography on a silica column with CH_2Cl_2 + hexane 1 + 1 as eluent. Due to the instability of the epoxide it was not possible to obtain a satisfactory elemental analysis. MS: *m/e* (%), 254 (85 %) M^+; 225 (78); 189 (100). The ^1H NMR spectrum was ambiguous, and therefore a ^{13}C NMR spectrum was recorded. Signals relative to TMS (ppm): C^5, 57.6; C^{12}, 59.7. In the spectrum determined with the off resonance technique C^5 showed a singlet and C^{12} a triplet.

3-Chloro-10,11-dihydro-5H-dibenzo[a,d]*cycloheptene (10)*. A mixture of the ketone *4* (121 g, 0.5 mol), 50 g of red phosphorus and 400 ml of hydriodic acid (57 %) was heated under reflux for 16 h. After cooling, water and ether were added and the mixture was filtered through celite. The aqueous layer was further extracted with ether. The combined ether extracts were washed with Na_2CO_3 solution, $Na_2S_2O_3$ solution, water and dried ($MgSO_4$). The solvent was evaporated *in vacuo*. The resulting viscous oil crystallized on standing, and was recrystallized from MeOH (charcoal) affording 93 g (82 %) of colourless crystals, m.p. 62–63 °C. Anal. ($C_{12}H_{13}Cl$) C, H, Cl.

3-Chloro-10,11-dihydro-5H-dibenzo[a,d]*cycloheptene-5-carboxaldehyde diethyl acetal (11)*. To a solution of *10* (86 g, 0.38 mol) in 500 ml of dry THF a solution of BuLi in hexane, 2.1 M (180 ml, 0.38 mol) was added dropwise with stirring during 1 h under oxygen-free nitrogen at room temperature. The dark red solution was stirred for another hour. Then a solution of diethyl phenyl orthoformate [5] (78 g, 0.40 mol) in 250 ml of dry THF was added dropwise during 1/2 h. The solution was heated under reflux for 2 h. After cooling, water and ether were added to the dark blue solution. The organic layer was washed with water, brine and dried ($MgSO_4$). After evaporation of the solvent the residual oil (137 g) was distilled under reduced pressure, b.p. 165–170 °C/7 Pa. Yield 95 g (76 %). The material crystallized on standing, m.p. 33–36 °C. Anal. ($C_{20}H_{23}ClO_2$) C, H, Cl, O.

3-Chloro-10,11-dihydro-5H-dibenzo[a,d]*cycloheptene-5-carboxylic acid (12)*. A solution of the carbanion of *10* was prepared as described for the preparation of compound *11* from *10* (23 g, 0.1 mol) in 100 ml of dry THF. Still under nitrogen this solution was poured through a teflon tube on to a slurry of dry ice in dry ether. After evaporation of the dry ice, water was added and the aqueous phase washed twice with ether and acidified with concentrated HCl. The precipitate was filtered off, washed with water and dried. Recrystallization from AcOH gave 18.7 g (68 %) of the acid, m.p. 159–160 °C. The acid and acyl chloride have been mentioned as starting materials in patents, *e.g.* Ref. 8, but no physical data were given. Anal. ($C_{16}H_{13}ClO_2$) C, H, Cl, O.

3-Chloro-10,11-dihydro-5H-dibenzo[a,d]*cycloheptene-5-carbonyl chloride (13)*. The acid (13.6 g, 0.05 mol) described above was dissolved in 50 ml of $SOCl_2$ and the solution was stirred

overnight at room temperature. The $SOCl_2$ was evaporated, the last traces being removed by evaporation together with added benzene. The remaining solid was recrystallized from heptane affording 12.1 g (83 %) of the acyl chloride, m.p. 84–85 °C. Anal. ($C_{16}H_{12}Cl_2O$) C, H, Cl, O.

Reduction of 13. Hydrogen was passed through a mixture of the acyl chloride *13* (2.9 g, 0.01 mol), 0.1 g of 10 % $Pd/BaSO_4$ and 0.02 ml of "Quinoline-S" in 50 ml of dry xylene heated to reflux. After about 3 h the evolution of HCl ceased and the mixture was filtered hot through celite, washed with $NaHCO_3$ solution and dried ($MgSO_4$). Evaporation of the solvent gave 2.5 g of a crystalline mass. Recrystallization from toluene afforded 2.1 g of compound *14*, m.p. 267–268 °C. The IR spectrum indicated the absence of carbonyl groups. NMR (C_6D_6): δ 2.4–3.5 (8 H, m), 4.6 (2 H, s), 6.4–7.2 (14 H, m). MS, *m/e* (%): 454 (< 1 %, M^+), 227 (100 %).

5,5'-Bis[3-chloro-10,11-dihydro-5H-dibenzo-[a,d]*cycloheptene] (14).* A solution of 3,5-dichloro-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene [6] (5.26 g, 0.02 mol) in 25 ml of dry THF was added dropwise under nitrogen to a stirred solution of the lithium salt of *10* prepared from *10* (4.56 g, 0.02 mol) as described for compound *11*. After the addition, the solution was heated under reflux for 2 h. The solution was cooled and diluted with ether and water and then filtered giving 1.9 g of *14*. The organic phase was washed with water and dried ($MgSO_4$). Evaporation of the solvent afforded a second crop (3.2 g). Crystallization from toluene gave 4.5 g of compound *14*, m.p. 267–268 °C. This material was identical with that obtained in the attempted Rosenmund reaction described above in the following respects: mixed melting point (266–267 °C), IR and NMR spectra.

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