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Preparation, Absolute Configuration and Conformation of Some α-Aryl-2-pyridylmethanols

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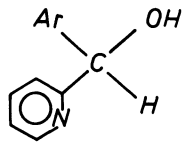
The syntheses of five optically active α-aryl-2-pyridylmethanols **1**—**5** are described. It is shown by means of chemical correlation with the known (−)-(α *R*,2*S*)-α-phenyl-2-piperidylmethanol **6** that all levo-rotatory isomers of **1**—**4** are of R configuration. It is also found via the relative integral intensities in the infrared spectra of the bands due to free and intramolecularly bonded hydroxyl groups in the compounds **1**—**4** and the free hydroxyl groups in the model compounds **7**—**10**, that the population of the conformers with an intramolecular OH···N bond in compounds **1**—**4** exceeds 80%.

In continuation of our investigations on the preparation, absolute stereochemistry and chiroptical properties of chiral 1,2-disubstituted 1,2-diarylethanes[1,2] were recently undertaken studies employing as models compounds containing two geminal aromatic carbo- or hetero-cyclic chromophores.

We presently wish to report the results from the preparation of a series of chiral α-aryl-2-pyridylmethanols **1**—**5** as well as data on their absolute configuration and preferred conformations obtained by means of chemical correlation and infrared spectroscopy. Our circular dichroism investigations require the stereochemical structure of the above mentioned compounds to be reliably known as the aim is the elucidation of some general relationships between molecular chirality and aromatic Cotton effects in compounds with geminal phenyl and pyridyl chromophores at the chiral center. It is known that such molecular moieties are present in important biologically active compounds with clearly observable biostereoselectivity.[3]



1 Ar = C_6H_5
2 Ar = 2-ClC_6H_4
3 Ar = 4-ClC_6H_4
4 Ar = 2,6-$Cl_2C_6H_3$
5 Ar = 4-$CH_3OC_6H_4$

Scheme 1.

Results and Discussion

Synthesis of the Racemic Methanols 1—5. Various approaches exist in the literature regarding the preparation of the racemic methanols **1**—**5**.[4-10] Among the most convenient ones is the procedure developed by Gilman and Spatz[10a] based on the interaction of 2-pyridyllithium with the corresponding aromatic aldehyde. In the present case the reaction was conducted at −78 °C, a temperature considerably lower than the recommended, leading to the racemic methanols **1**—**5** in yields significantly better than those reported for analogous compounds (see Experimental).

Preparation of the Optically Active Methanols. Among all presently considered methanols **1**—**5** only compound **1** was found described in an optically active form.[11-13] This compound resolved by Davies with (+)-tartaric acid[11] and considered as the pure levo-rotatory isomer[12-14] was found in the present investigations to be optically impure (see below).

The racemic methanols **2** and **4** were successfully resolved by means of (+)-tartaric acid, while the racemic **3** was resolved by means of (−)-*O*,*O*′-dibenzoyltartaric acid.

The optically active methanol **1** was obtained by dehalogenating samples of (+)-**2**, (−)-**3**, and (+)-**4** of highest purity by treatment acc. ref.[15] with hydrazine hydrate in the presence of palladium over charcoal. In all three cases the obtained samples of **1** showed at λ=589 nm in chloroform practically the same absolute value of the specific rotation i.e. +162.9°, −161.5°, and +162.8°. It can be seen that these values agree very well among themselves while on the other hand they considerably exceed the reported ones for **1** by other authors i.e. $[\alpha]_{589}=-86.2°$ [11] and $[\alpha]_{589}=-108°$.[12]

It can thus be concluded that in the present investigations the racemates of **2**, **3**, and **4** were completely resolved, while the previously reported resolution of (±)-**1** with (+)-tartaric acid[11,12] indeed afforded a product of 50—70% optical purity.

The resolution of (±)-**5** offered considerable difficulties, the best result being obtained with (+)-camphor-10-sulfonic acid. Repeated recrystallization of the diastereoisomeric sulfonates afforded insufficiently pure free base **5** which had to be subjected to additional fractional recrystallization in order to remove the less soluble (±)-**5** finally leading to the desired optically pure **5**.

Absolute Configuration. The possibilities for the application of chemical correlation are rather restricted since only a few chiral compounds with geminal aryl and pyridyl groups with reliable absolute configuration have hitherto been reported.[3a,16]

Employing the chemical transformation approach and circular dichroism Pohl and Wollweber recently compared the absolute configuration of (−)-ephedrine and (−)-*erythro*-α-phenyl-2-piperidylmethanol **6**.[17] In this much more reliable way they corroborated the earlier assumption made by Fauley and LaPidus[18] that (−)-*erythro*-**6** is of (α*R*,2*S*) configuration. On the ground of this conclusion and the earlier results[12,14] regarding the conversion of (−)-α-phenyl-2-pyridylmethanol on catalytic hydrogenation into (−)-*erythro*-**6** it can be assumed that the chiral center in (−)-**1** is of R configuration.

In the conversion of (−)-**1** into (−)-**6** carried out by other researchers[12,14] samples of low optical purity have been used and the absence of *threo*-**6** in the products had not been experimentally determined. For this reason we subjected the presently obtained (−)-**1** with $[\alpha]_{578}=-169.5°$ (chloroform) to catalytic hydrogenation. The thin-layer chromatographic analysis of the crude reaction mixture revealed indeed the presence of the two expected diastereoisomers. From this mixture was successfully isolated in pure form only the predominating *erythro*-**6** isomer with $[\alpha]_{578}=-53.2°$(chloroform). The comparison of the data obtained in the present study for (−)-**1** and (−)-*erythro*-**6** with the reported ones[14] for (−)-**1** $[\alpha]_{578}=-113°$(chloroform) and for (−)-*erythro*-**6** $[\alpha]_{578}=-35.3°$(chloroform) shows that the two samples described earlier have been only of about 65% optical purity. The (α*R*, 2*S*) absolute configuration of the (−)-*erythro*-**6** is in agreement with data obtained recently in circular dichroism studies conducted on molybdenum and rhodium complexes of (−)-**6** formed in situ.[19]

On the other hand the chemical conversions conducted of (+)-**2** to (+)-**1**, of (−)-**3** to (−)-**1**, and of (+)-**4** to (+)-**1**, respectively, which obviously proceed without affecting the absolute configuration,[1b,15] allow the correlation of the absolute configurations also of the three presently obtained chlorine-containing methanols **2**—**4**. In this manner to all the levo-rotatory isomers of **1**—**4** should be assigned R configuration.

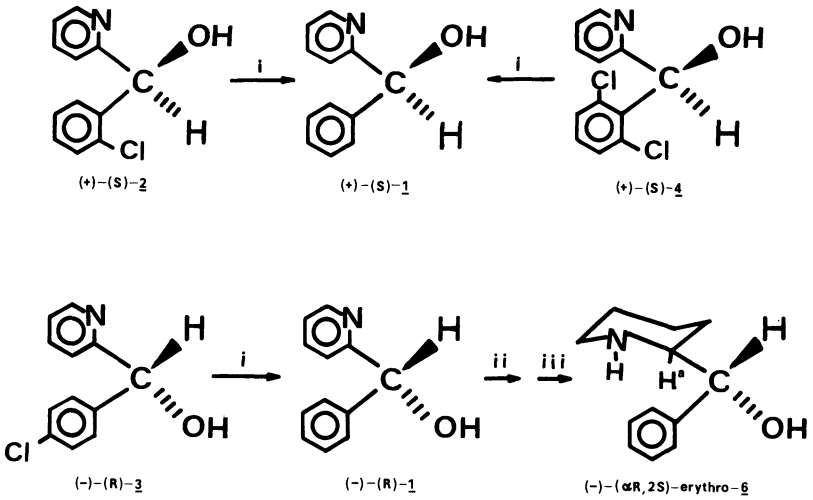
For the correlation of the absolute configuration of (−)-**5** CD method turned out to be the most convenient way. On the basis of the observed exciton coupling between the benzene and 2-pyridine chromophores of a series α-aryl-2-pyridylmethane derivatives we ascribed recently to the levo-rotatory isomer of **5** also the R configuration.[20]

Infrared Spectra. The infrared spectra of the compounds studied (**1**—**4**) give evidence for the existence of at least two conformations, one of them being intramolecularly hydrogen bonded. The task of this study consists in calculating statistical weights of these two conformations in order to give preference to one of them.

The relative populations of mobile conformational equilibria between conformers with bonded and nonbonded hydroxyl groups can be evaluated from the integral intensities (*B*) of the free OH band whose molar absorptivity has been taken from suitably chosen model compounds without intramolecular hydrogen bond.[21] Many reasons reject the use of the bonded OH band.[22] The mole percentage of the bonded conformation is simply derived by subtracting the mole percentage of the free one from 100%.

The IR spectral data are listed in Table 1. Besides the presently studied α-aryl-2-pyridylmethanols it also includes the corresponding 3- and 4-pyridyl-containing compounds used as models. The spectra were taken in 1×10^{-3} mol dm^{-3} carbon tetrachloride solutions in a 5 mm NaCl cell.

The relative error in the determination of the mole percentage of the free and bonded conformations mainly reflects the accuracy of the *B* values for the



Scheme 2. i $NH_2NH_2\cdot H_2O$, Pd/C; ii H_2, PtO_2; iii Separation of mixture erythro+threo, TLC analyse.

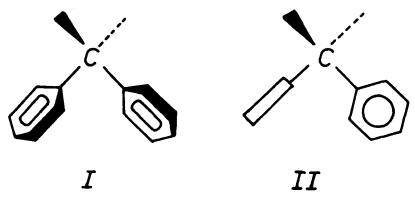
Table 1. IR Spectral Data from Diluted (1×10^{-3} mol dm^{-3}) CCl_4 Solutions of α-Aryl-2-pyridylmethanols

Intramolecularly Bonded α-Aryl-2-pyridylmethanols								α-Aryl-3- or 4-Pyridylmethanols		
Compd No.	ν_{OH}/cm^{-1} Free	ν_{OH}/cm^{-1} Bonded	Band area(B) l mol^{-1} cm^{-2} free OH	Band area(B) l mol^{-1} cm^{-2} bonded OH	% free OH	% OH···N	% OH···Cl	Compd[b] No.	ν_{OH}/cm^{-1} free	Band area(*B*) l mol^{-1} cm^{-2} free OH
1	3620	3408	508	2689	22	78	—	7	3618	2280
2	3616	3398	142	1837	9	91	—	8	3618	2276
3	3620	3404	292	2067	15	85	—	9	3616	1642
4	3618	3413	104	3370	6	91	3	10	3618	1912
		3579[a]		128				11[c]	3618	634

a) Bond OH···Cl. b) α-Phenyl-3-pyridylmethanol (**7**), α-Phenyl-4-pyridylmethanol (**8**), α-(2-Chlorophenyl)-3-pyridylmethanol (**9**), α-(4-Chlorophenyl)-3-pyridylmethanol (**10**), α-(2,6-Dichlorophenyl)-3-pyridylmethanol (**11**). c) The *B* value for OH···Cl band is 2570.

studied sample and the reference model compounds. The structural isomers containing 3- and 4-pyridyl groups **7**—**11** were chosen as standard compounds free of intramolecular OH···N bonding. The conformational distribution of compound **1** was determined employing **7** and **8** as models. The difference between the calculated B values of these two compounds was 4 units which renders the error in the evaluation of the conformational distribution below 1%. For this reason the conformational populations of the remaining compounds **2**—**4** were evaluated using one standard compound with free hydroxyl group — the corresponding α-aryl-3-pyridylmethanols.

The study of the mole percentage of the conformational populations of compounds **1**—**4** given in Table 1 leads to the conclusion that the greatest statistical weight (above 80%) should be ascribed to conformations with bonded hydroxyl functions. The introduction of a chlorine atom in an ortho position, compound **2**, increases the statistical weight of the intramolecularly bonded conformer by 13%. The effect of the chlorine atom in para position, compound **3**, in comparison with the ortho isomer appears to be less pronounced because of the lack of steric hindrance. The difference in the conformational populations of compound **1** and **3** is too small to seek for an explanation. They have been expected to give rise to nearly equal populations. The corresponding differences for **1** and **2** (respectively, 4) obviously reflect the presence of the voluminous chlorine atoms in the ortho positions. The helical (I) and the perpendicular (II) conformations are the two



I *II*

Scheme 3.

conformations that diarylmethanes may assume. The helical conformation is considered to be the preferred one in the solid state, while the data in solution are ambiguous.[23] Most probably the helical conformations are the preferred ones for compounds **1**—**4**, and the ortho substitution further diminishes the population of perpendicular and other forms.[24]

Compound **4** with two chlorine atoms in ortho positions deserves a special attention. Its IR spectrum shows weakening of the OH···N bonding and a presence of a second weak OH···Cl bond at 3579 cm^{-1},[27,28] thus indicating the existence of three conformations: A - without intramolecular hydrogen bonding, B - with an OH···N bonding and C - with an OH···Cl bonding. The contributions of these three conformations will be separately considered for the sake of clarity.

The IR spectrum of compound **11** used as a reference, however, contains two bands: A free OH band at 3618 cm^{-1} and a second one at 3579 cm^{-1} due to OH···Cl bonding. The correct use of these bands as standards requires an estimation of their relative populations. Firstly we calculated the mole percentage of the free OH population. This quantity could be determined employing the *B* value of compound **9** as a 100% free OH standard. A value of 39% free OH population for compound **11** was obtained in this way. Using this value and the *B* values of the free OH bands of compounds **4** and **11** we found 6% for the population of the conformation A of compound **4**. The remaining quantity of 94% is distributed among the conformations B and C. The contribution of the conformation C could be approximately estimated using the *B* value (2570) for the OH···Cl band of compound **11** taken as a standard. The relative population of this bonded conformation was found to be 61%. On this basis a value of ca. 3% is obtained for the conformation C in compound **4**. The remaining 91% should be ascribed to the OH···N bonded conformation B which appears to be the most populated one.

Experimental

The mp (on a Kofler apparatus) are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 instrument. IR spectra were recorded on a Bruker IFS 113V instrument. TLC analyses of compound **1**—**5** were performed on plates coated with silica gel DG (Riedel de Haën, Hanover) using benzene:chloroform:methanol=6:4:1 as a solvent system.

Syntheses of the Racemic α-Aryl-2-pyridylmethanols (1—5) and Their Resolution. General Procedure. To a stirred ethereal solution of 2-pyridyllithium prepared by the halogen-interconversion method (see Refs. 9, 10) from 2-bromopyridine (38 g, 240 mmol) and butyllithium (4.25 g, 600 mmol Li and 41 g, 300 mmol butyl bromide) at −78 °C was added dropwise during 45 min (while the temperature was allowed to rise to −30 °C) the freshly-distilled aromatic aldehyde (120 mmol) dissolved in about 150 ml dry ether. The mixture was stirred for another 1.5 h at the same temperature, hydrolyzed carefully with 25 ml water and worked-up as usual. The isolated crude reaction product was purified as a base or after conversion into hydrochloride.

α-Phenyl-2-pyridylmethanol (1). (±)-**1**: Prepared according to the general procedure. Recrystallization from methanol of the crude base gave the pure (±)-**1** (16.4 g, 74%), mp 74—76 °C (lit,[4,5] mp 76—78 °C).

α-(2-Chlorophenyl)-2-pyridylmethanol (2). (±)-**2**: The crude hydrochloride was recrystallized from MeOH-Et_2O affording 25.4 g (83%) pure (±)-**2**·HCl, mp 170—174 °C (with decomposition) (lit,[4] mp 174—175 °C). Mp of free base 62—64.5 °C (lit,[5,8] mp 63—65 °C).

(+)-**2**: A hot solution of 10.98 g (±)-**2** and 7.50 g (+)-tartaric acid in 130 ml *i*-PrOH was allowed to cool slowly to room temp and then kept at this temp for another 24 h. The resulting crystalline product (10.10 g, mp 133—144 °C) was recrystallized three times with 8 ml *i*-PrOH for each gram of salt to give 5.11 g of crystals, mp 145—147 °C and $[\alpha]_D^{17}$ +28.2° (*c* 1.2, MeOH). After two additional recrystallizations the samples of the corresponding free base (oil) possess practically the same $[\alpha]_D^{17}$ values: +242.8° (*c* 0.5, $CHCl_3$). Yield of (+)-**2** was 2.20 g (40%).

α-(4-Chlorophenyl)-2-pyridylmethanol (3). (±)-**3**: After one recrystallization of the crude **3**·HCl from MeOH-Et_2O and one of the free base from EtOAc 20.2 g (77%) pure (±)-**3** was obtained with mp 82.5—84 °C (lit, mp 80—81 °C,[5] 83 °C[6]).

(−)-**3**: From a solution of 3.30 g (±)-**3** and 5.37 g (−)-*O,O'*-dibenzoyltartaric acid in 25 ml hot *i*-PrOH after slow cooling and standing for 24 h at room temp 3.14 g salt (mp 141—144 °C) was collected and subjected to two additional recrystallizations from 7 resp. 6 ml *i*-PrOH. Yield of the crystalline salt was 1.80 g, mp 145—148 °C, $[\alpha]_D^{17}$ −80.1° (*c* 0.6, MeOH). The corresponding free base mp 95—97 °C, $[\alpha]_D^{17}$ −123.2° (*c* 0.5, $CHCl_3$). After two further recrystallizations of the salt the optical rotation of the liberated base reached $[\alpha]_D^{13}$ −131.1° (*c* 0.5, $CHCl_3$), which value increased after two more recrystallizations of the salt to $[\alpha]_D^{16}$ −132.5° (*c* 0.7, $CHCl_3$).

α-(2,6-Dichlorophenyl)-2-pyridylmethanol (4). (±)-**4**: The pure **4**·HCl after recrystallization of the crude salt from MeOH-Et_2O (yield 28.7 g, 83%, Anal. ($C_{12}H_{10}Cl_3NO$) C, H, Cl) was converted into the free base (±)-**4**, mp 76—78 °C (lit,[7,8] mp 79.5—82 °C).

(+)-**4**: 5.08 g (±)-**4** and 3.00 g (+)-tartaric acid were dissolved in 75 ml of refluxing *i*-PrOH and then allowed to stand. After about 10 d by spontaneous crystallization at room temp 1.27 g crystals were collected. The further recrystallization of this crystalline product from *i*-PrOH (15 ml) afforded after 1 d at room temp 0.12 g of salt (3%), mp 105—108 °C and $[\alpha]_{546}^{19}$ +189.1° (*c* 0.4, MeOH). The corresponding free base (oil) with $[\alpha]_D^{19}$ +182.9° (*c* 1.0, $CHCl_3$) on hydrogenolysis to (+)-**1** found to be optically pure.

α-(4-Methoxyphenyl)-2-pyridylmethanol (5). (±)-**5**: After recrystallization of the crude base from EtOAc 12.94 g (50%) (±)-**5** with mp 131.5—133 °C (lit,[3] mp 133—134 °C) was obtained.

(−)-**5**: 4.30 g (±)-**5** and 4.00 g (+)-camphor-10-sulfonic acid were dissolved in 50 ml refluxing *i*-PrOH. After six recrystallizations from *i*-PrOH (salt(g):*i*-PrOH(ml)=1:6) the resulting crystalline salt with mp 144—147 °C and $[\alpha]_D^{16}$ −0.1° (*c* 0.5, MeOH) was found to be only partially resolved. The corresponding optically impure base with $[\alpha]_D^{16}$ −24.8° (*c* 0.7, $CHCl_3$) was recrystallized several times from EtOAc by which procedure only from the third mother liquor 90 mg (4%) of the levo-rotating isomer, mp 70.5—72 °C and $[\alpha]_D^{16}$ −139.2° (*c* 0.7, $CHCl_3$) was isolated.

Convesion of the Optically Active Chlorine-Containing Methanols 2—4 into α-Phenyl-2-pyridylmethanol 1. General Procedure. The chlorine containing methanol (1 mmol) dissolved in 10 ml dry EtOH was refluxed for 5 min in the presence of 2 ml of hydrazine hydrate (98%) and 70 mg of Pd/C (10%).[15] The catalyst was filtered off, washed with EtOH and the combined filtrates evaporated to dryness. The resulting oil was taken up in $CHCl_3$ and washed with water. The residue after removing the chloroform is the practically TLC pure methanol **1**. A recrystallization from light petroleum afforded **1** as colorless crystals.

Conversion of (+)-2 into (+)-1. From 450 mg (+)-**2** with $[\alpha]_D^{17}$ +242.8° (*c* 0.5, $CHCl_3$) according to the general procedure 266 mg (70%) of pure (+)-**1**, mp 63—67 °C and $[\alpha]_D^{17}$ +162.9° (*c* 0.4, $CHCl_3$), was obtained after recrystallization.

Conversion of (−)-3 into (−)-1. 220 mg (−)-**3** with $[\alpha]_D^{17}$ −132.5° (*c* 0.7, $CHCl_3$) in the same manner afforded 132 mg (71%) pure (−)-**1**, mp 64.5—66 °C and the following values for the optical rotation in chloroform: $[\alpha]_D^{16}$ −161.5° (lit, −86.2°,[11] −108°[12]), $[\alpha]_{578}^{16}$ −169.5° (lit,[14] −113°), $[\alpha]_{546}^{16}$ −197.0° (lit,[11] −104.7°).

Conversion of (+)-4 into (+)-1. From 221 mg of (+)-**4** with $[\alpha]_D^{23}$ +182.9° (*c* 0.5, $CHCl_3$) according to the general procedure after recrystallization pure (+)-**1** (62 mg, 39%), mp 64—67 °C and $[\alpha]_D^{17}$ +162.8° (*c* 0.4, $CHCl_3$), was obtained.

Catalytic Hydrogenation of (−)-1 to (−)-*erythro*-(*αR, 2S*)-α-Phenyl-2-piperidylmethanl (6). 2.44 g (11 mmol) of (−)-**1**·HCl ($[\alpha]_D^{17}$ −215.0° (*c* 0.4, MeOH), corresponding base: $[\alpha]_D^{17}$ −162.8° (*c* 0.4, $CHCl_3$)) dissolved in 100 ml dry EtOH in the presence of 70 mg of PtO_2 was hydrogenated according to Ref. 12a in a rotating laboratory autoclave at 5.5 atm and room temp. After the consumption of 36.3 mmol of H_2 (in about two hours and a half) the catalyst and the

solvent were removed. The resulting mixture containing the two optically active diastereoisomeric α-phenyl-2-piperidylmethanol hydrochlorides was subjected to separation by twofold recrystallization from abs EtOH–Et_2O[29] to give 1.24 g (51%) of (−)-*erythro*-**6**, mp 212—216 °C and $[\alpha]_D^{17}$ −32.2° (*c* 0.6, H_2O), $[\alpha]_D^{17}$ −12.4° (*c* 0.3, $CHCl_3$). TLC analysis of the corresponding free base: One spot (silica gel; Et_2O:MeOH=17:3) was found to be free from the threo isomer. At the same conditions TLC analysis of the crude reaction mixture gave two spots with $R_{f(erythro)}$=0.13 and $R_{f(threo)}$=0.21.

The free base of (−)-*erythro*-**6** had mp 127—130 °C and $[\alpha]_D^{17}$ −50.8°, $[\alpha]_{578}^{17}$ −53.2° (*c* 0.4, $CHCl_3$). Lit mp and optical rotation for (−)-*erythro*-**6**·HCl 213.5—215 °C, $[\alpha]_D$ −22.0° (H_2O),[18] $[\alpha]_D$ +7.0° ($CHCl_3$)[12] and for (−)-*erythro*-(α*R*,2*S*)-**6**-base −132—133°C, $[\alpha]_{578}$ −35.3° ($CHCl_3$).[14,17]

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24) A molecular mechanics study of the basic compound **1** revealed that *helical* conformers also are the most populated local minima of **1** in the absence of intramolecular hydrogen bonding.[25] Two among three of them possess an N–C(Py)–C^{al}–O skeleton suitably dispositioned for an intramolecular hydrogen bond formation. *Perpendicular* and other local minima are of energy higher than 0.7 kcal mol^{-1}(1 cal=4.184 J) above the global minimum helical conformer.

25) The calculations were carried out with the MM2 force field.[26] A potential function to simulate intramolecular hydrogen bond formation is not included in the present version of MM2, and the results has to be considered only as an approximate estimation of the conformational preferences in the absence of intramolecular hydrogen bonding. Calculational details are available on request from the authors.

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