ASYMMETRIC REACTIONS. XLVI.*

ABSOLUTE CONFIGURATION OF α,β,γ-SUBSTITUTED METHYLPYRIDYLMETHANOLS AND METHYLPYRIDYLMETHYLAMINES

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The absolute configuration of all three isomeric methylpyridylmethylamines *IIIa*–*IIIc* and methylpyridylmethanols *IVa*–*IVc* has been determined by the methods of asymmetric transformation and chemical correlation as well as by the analysis of the optical rotatory dispersion curves.

For the study of the relations between the absolute configuration of compounds, having besides an heteroaromatic ring[1–3] a centre of chirality, and the shapes of their rotatory dispersion and circular dichroism curves, we have now prepared all isomeric alcohols and amines which have in their molecule the pyridine ring in optically active form and determined their absolute configuration. As starting materials we have used the isomeric acetylpyridines prepared by Claisen condensation of the ethyl esters of the corresponding pyridine carboxylic acids and subsequent ketonic hydrolysis of the resulting β-keto esters. Whilst the reduction of 3- and 4-acetylpyridine with lithium aluminium hydride afforded in good yield methyl-3-pyridylmethanol (*Ib*) and methyl-4-pyridylmethanol (*Ic*) respectively, in the reduction of 2-acetylpyridine the pyridine ring was also partially reduced, and the expected product formed only in low yield was accompanied by a number of by-products. Only the catalytic hydrogenation over palladium adsorbed on charcoal provided the required methyl-2-pyrridylmethanol (*Ia*) in good yield. The amines *IIa*–*IIc* (R = H) were prepared by reduction of the oximes of the acetylpyridines with zinc and acetic acid. Lately, these amines have also been obtained by the Wallach–Leuckart reduction[4]. From the primary amines were prepared by treatment with formyl acetate the N-formyl derivatives *IIa*–*IIc* (R = CHO) which were reduced with lithium aluminium hydride to the secondary amines *IIa*–*IIc* (R = CH_3). The alcohols *Ia* and *Ib* were resolved into their optical antipodes with dibenzoyltartaric acid, and alcohol *Ic* as well as the amines

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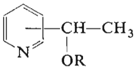
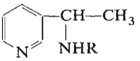
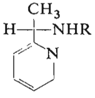
IIa–*IIc* (R = H) with tartaric acid. The absolute configuration of the amines *IIIa* to *IIIc* (R = CH_3) was determined by the method of the asymmetric transformation[5,6]. From the reactions of (*S*)-(+)-hydratropic acid with the amines *IIa*–*IIc* (R = CH_3) we isolated the unreacted laevorotatory amines. Under the assumption that the pyridine ring behaves in this type of reaction as a more bulky substituent than the methyl group, and on the basis of the already earlier inferred configurational relations, belongs to these amines the absolute configuration *S* depicted by the projection formulae *IIIa*–*IIIc* (R = CH_3). The absolute configuration of the amines *IIIa*–*IIIc* (R = H) has been further determined by the chemical correlation by means of ozonisation of the acetyl derivatives *IIIa*–*IIIc* (R = $COCH_3$) followed by further oxidation of the products to (*S*)-(−)N-acetylalanine (*IV*).



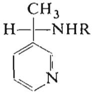
Ia–*Ic*



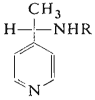
IIa–*IIc*



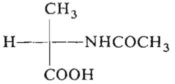
IIIa



IIIb

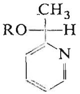


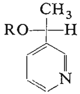
IIIc

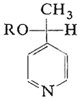


IV

The comparison of the optical rotation of substances structurally related and with each other correlated by the chemical route indicated some close relations between the sense of rotation and the atom distribution in the molecule. Thus, with alkylarylmethanols and alkylarylmethylamines, where the optically active chromophore is the aromatic ring, it has for instance been shown that, in accord with their ultraviolet spectra, the shape of the ORD and CD curves is very similar. All dextrorotatory alcohols and amines of the absolute configuration *R* exhibit in the region of the ^1L_b band between 250 and 270 nm a multiple negative Cotton effect superposed on a positive basic curve[7]. In connection with the extension of these findings, we have measured the ORD curves of the amines *IIIa*–*IIIc* (R = H and CH_3, resp.) and alcohols *IVa*–*IVc* (R = H) (all in ethanol). The ORD curves of these compounds show in the region of 240–270 nm a multiple Cotton effect. The amine *IIIa* and the alcohol *IVa* of opposite absolute configuration exhibit, as expected, opposed Cotton effects, in the case of amine *IIIa* (R = H or CH_3) a positive and in the case of alcohol *IVa* (R = H) a negative Cotton effect. Fodor[8] found for the chemically correlated (*R*)-(−)-ethyl-2-pyridylmethanol also a negative Cotton effect. Hence, the dextrorotatory alcohol *IVa* (R = H) has the absolute configuration *R*, and by measurement was confirmed the configuration of the amines *IIIa* (R = H and CH_3, resp.). In the case of the amines and alcohol in β-position of the pyridine ring has been observed with the amines *IIIb* (R = H and CH_3, resp.) a negative and with alcohol *IVb* (R = H) a positive Cotton effect. The alkaloids (*S*)-(−)-nicotine and (*S*)-(−)-anabasine show in this region also a negative Cotton effect[9]. The configuration of the alcohol determined by us confirms the absolute configuration of (*S*)-(−)-methyl-3-pyridylmethanol, lately determined by the method of Horeau and by analysis of the CD curves[10]. Similarly, also the amine *IIIc* (R = H and CH_3, resp.) exhibits a negative Cotton effect which is shifted to shorter wave-length. The ORD curve of the alcohol *IVc* (R = H) could be measured only orientatively on account of the small rotation and high absorption in the ultraviolet region.


IVa


IVb


IVc

The results obtained corroborate the fact established by us that it is feasable to compare the ORD curves of structurally similar alcohols and amines and thus to assign the absolute configuration to the alcohols *IVa*–*IVc* (R = H). The opposite Cotton effect of the 2-substituted pyridine derivatives in comparison with that of the 3- and 4-substituted derivatives possessing the same absolute configuration may be attributed to the formation of a hydrogen bond between the OH, NH_2 and $NHCH_3$ group, respectively and the nitrogen atom in the pyridine ring of the 2-substituted compounds, which prefers a particular conformation. From the literature it is known[11] that hindered rotation (in extreme cases by ring formation) causes at the same absolute configuration an opposite Cotton effect. For this fact speaks the presence of a hydrogen bond, as proved by the infrared spectra, as well as the dependence of the ORD and CD curves on the solvent used. In order to prevent the formation of the hydrogen bond, we prepared the acetyl derivatives of the amines *IIIa*–*IIIc* (R = H) and alcohols *IVa*–*IVc* (R = H). As expected, the acetyl derivatives *IIIa*–*IIIc* (R = $COCH_3$) of the amines which possess the same absolute configuration exhibit a negative Cotton effect regardless of the position of the pyridine ring, and the acetyl derivatives *IVa* and *IVb* (R = $COCH_3$) of the alcohols possessing the opposite absolute configuration exhibit a positive Cotton effect.

EXPERIMENTAL

Melting and boiling points are uncorrected. Samples for analysis were dried in an oil-pump vacuum at room temperature for 8 h. Optical rotations were measured on a polarimeter with an accuracy of 0·02°. ORD curves were taken on the Jasco UV-5 apparatus. 2-Acetylpyridine[12], b.p. 67—67·5°C/9 Torr, 3-acetylpyridine, b.p. 105°C/16 Torr, and 4-acetylpyridine[13], b.p. 103°C/18 Torr, m.p. 14·5°C, were prepared by Claisen condensation of the ethyl esters of pyridine carboxylic acids.

(*S*)-(—)-Methyl-2-pyridylmethylamine (*IIIa*, R = H)

The racemic amine *IIa* (R = H), b.p. 74°C/10 Torr, was prepared by reduction of 2-acetylpyridine oxime, m.p. 119—121°C, with zinc and acetic acid[14] in 82% yield; acid tartrate m.p. 163—164°C (water), $[\alpha]_D^{20}$ +5·10° (*c* 4·02, water). Base b.p. 83°C/14 Torr, $[\alpha]_D^{20}$ —28·5° (*c* 5·71, ethanol). For $C_7H_{10}N_2$ (122·2) calculated: 68·82% C, 8·25% H, 22·93% N; found: 69·01% C, 8·35% H, 23·21% N. The acetyl derivative *IIIa* (R = $COCH_3$) was prepared from the amine *IIIa* (R = H), $[\alpha]_D^{20}$ —21·6° (ethanol), by action of acetic anhydride in benzene; m.p. 105—106°C (cyclohexane), $[\alpha]_D^{20}$ —95·1° (*c* 3·72, ethanol). Literature[15] gives for the racemate m.p. 107°C. For $C_9H_{12}N_2O$ (164·2) calculated: 65·83% C, 7·37% H, 17·06% N; found: 65·96% C, 7·41% H, 17·28% N.

(*S*)-(—)Methyl-3-pyridylmethylamine (*IIIb*, R = H)

The amine *IIb* (R = H), b.p. 104—105°C/16 Torr, prepared by reduction of 3-acetylpyridine oxime, m.p. 114—115°C, with zinc in acetic acid[16] was converted into the acid tartrate, m.p. 193—194°C (aqueous ethanol), $[\alpha]_D^{20}$ + 20·35° (*c* 4·01, water). Base b.p. 99°C/15 Torr, $[\alpha]_D^{20}$ — 39·4° (*c* 4·60, ethanol). For $C_7H_{10}N_2$ (122·2) calculated: 68·82% C, 8·25% H, 22·93% N; found: 68·81% C, 8·43% H, 23·27% N. The acetyl derivative *IIIb* (R = $COCH_3$) was prepared from the amine *IIIb* (R = H), $[\alpha]_D^{20}$ —8·86° (ethanol); m.p. 72—74°C, $[\alpha]_D^{20}$ —34·7° (*c* 6·06, ethanol). For $C_9H_{12}N_2O$ (164·2) calculated: 65·83% C, 7·37% H, 17·06% N; found: 65·91% C, 7·20% H, 17·30% N.

(*S*)-(—)-Methyl-4-pyridylmethylamine (*IIIc*, R = H)

The racemic amine *IIc*, b.p. 94—97°C/11 Torr (reported[1] b.p. 221—223°C), was prepared by reduction of 4-acetylpyridine oxime, m.p. 158—160°C, with zinc and acetic acid. Acid tartrate m.p. 205—207°C (water), $[\alpha]_D^{20}$ +18·15° (*c* 8·12, water). The free base boiled at 95°C/9 Torr, $[\alpha]_D^{20}$ —27·9° (*c* 7·44, ethanol). For $C_7H_{10}N_2$ (122·2) calculated: 68·82% C, 8·25% H, 22·93% N; found: 68·91% C, 8·51% H, 23·16% N. The acetyl derivative *IIIc* (R = $COCH_3$) was prepared from the amine *IIIc* (R = H), $[\alpha]_D^{20}$ —12·3° (ethanol); b.p. 147—150°C/0·05 Torr, m.p. 92—93°C, $[\alpha]_D^{20}$ —30·8° (*c* 4·22, ethanol). For $C_9H_{12}N_2O$ (164·2) calculated: 65·83% C, 7·37% H, 17·06% N; found: 66·02% C, 7·42% H, 17·25% N.

(*R*)-(—)-Methyl-2-pyridylmethanol (*IVa*, R = H)

The racemic alcohol, b.p. 95°C/10 Torr, was prepared by catalytic hydrogenation of 2-acetylpyridine over palladium adsorbed on charcoal in 98% ethanol at a pressure of 3 atm[17]. Acid dibenzyoltartrate m.p. 145—147°C (ethanol), $[\alpha]_D^{20}$ —93·3° (*c* 3·86, ethanol). Free base b.p. 96—97°C/14 Torr, $[\alpha]_D^{20}$ —56·6° (*c* 6·27, ethanol). For C_7H_9NO (123·2) calculated: 68·25% C, 7·37% H, 11·38% N; found: 68·34% C, 7·50% H, 11·74% N. The acetyl derivative *IVa* (R =

= $COCH_3$) was prepared from alcohol *IVa* (R = H) by action of acetic anhydride in pyridine; b.p. 67—70°C/0·2 Torr, $[\alpha]_D^{20}$ −91·5° (*c* 4·12, ethanol). Literature[18] gives for the racemic product b.p. 94°C/0·3 Torr. For $C_9H_{11}NO_2$ (165·2) calculated: 65·44% C, 6·71% H, 8·48% N; found: 65·68% C, 6·96% H, 8·72% N.

(*R*)-(+)-Methyl-3-pyridylmethanol (*IVb*, R = H)

The racemic alcohol, b.p. 128—129°C/10 Torr, prepared by reduction of 3-acetylpyridine with lithium aluminium hydride in ether[19] afforded on resolving with dibenzoyltartaric acid the salt melting at 126—127°C (ethanol). The base liberated from the salt boiled at 132°C/11 Torr, $[\alpha]_D^{20}$ +11·9° (*c* 4·54, ethanol). For C_7H_9NO (126·2) calculated: 68·25% C, 7·37% H, 11·38% N; found: 67·99% C, 7·66% H, 11·50% N. The literature gives for the rotation of the base obtained by resolving with tartaric acid $[\alpha]_D^{20}$ −56·3° (ethanol)[20] and $[\alpha]_D^{20}$ −40·2 (ethanol)[10].

(*R*)-(+)-1-Acetoxy-1-(3-pyridyl)ethane (*IVb*, R = $COCH_3$)

The title compound was prepared from alcohol *IVb* (R = H) in an analogue manner as in the foregoing experiment; b.p. 65—67°C/0·2 Torr, $[\alpha]_D^{20}$ +23·4° (*c* 5·20, ethanol). Literature[15] gives for the racemate b.p. 86°C/2 Torr.

(*R*)-(+)-Methyl-4-pyridylmethanol (*IVa*, R = H)

The racemic alcohol, b.p. 130—132°C/14 Torr, m.p. 56—57°C, obtained by reduction of 4-acetylpyridine with lithium aluminium hydride[16] was converted into the acid tartrate, m.p. 94—95°C (ethanol), $[\alpha]_D^{20}$ 8·15° (*c* 3·99, ethanol). The liberated base melted at 56—57°C, $[\alpha]_D^{20}$ +4·27 (*c* 4·68, ethanol). For C_7H_9NO (123·2) calculated: 68·25% C, 7·37% H, 11·38% N; found: 68·23H C, 7·58% H, 11·58% N.

Secondary Amines *IIa*—*IIc* (R = CH_3)

The amines *IIa*—*IIc* (R = CH_3) were prepared by reduction of the N-formyl derivatives *IIa*—*IIc* (R = CHO) with lithium aluminium hydride in ether. The formylation of the primary amines *IIa*—*IIc* (R = H) was performed with formyl acetate in benzene. Methyl-2-pyridylmethylaminomethane (*IIa*, R = CH_3), b.p. 81—85°C/14 Torr (literature[4] gives b.p. 60—64°C/3 Torr), was prepared by reduction of 1-formylamino-1-(2-pyridyl)ethane (*IIa*, R = CHO), b.p. 99—100°C/0·05 Torr (literature gives b.p. 156°C/4 Torr[19] and 129—131°C/3 Torr; ref.[4]). Methyl-3-pyridylmethylaminomethane (*IIb*, R = CH_3), b.p. 93—95°C/12 Torr (literature[4] gives b.p. 60—64°C/3 Torr), was prepared by reduction of compound *IIb* (R = CHO), b.p. 124—128°C/0·07 Torr (literature[4] gives b.p. 170—172°C/14 Torr). Methyl-4-pyridylmethylaminomethane (*IIc*, R = = CH_3), b.p. 83—85°C/15 Torr (literature[4] gives b.p. 110—112°C/21 Torr) was obtained by reduction of compound *IIc* (R = CHO), b.p. 145—150°C/0·07 Torr (literature[4] gives b.p. 175—180°C/1·5 Torr).

Ozonisation

Through a solution of the acetyl derivative *IIIa*—*IIIc* (R = $COCH_3$) (4 g) in 50 ml of tetrachloromethane, ozonised oxygen was bubbled for 30 h at −10°C. The solution was then boiled with 30 ml of 15% NaOH and 10 ml of 30% hydrogen peroxide. The aqueous layer was neutralised with 20% hydrochloric acid and evaporated to dryness. The residue was extracted with hot ethanol, and the N-acetylalanine obtained after evaporation was crystallised from ether–benzene. Compound *IIIa* (R = $COCH_3$) afforded (*S*)-(−)-N-acetylalanine, m.p. 116—118°C, $[\alpha]_D^{20}$ −20·5° (*c* 5·50, water, compound *IIIb* (R = $COCH_3$) the product with m.p. 118—119°C, $[\alpha]_D^{20}$ −9·8° (*c* 6·64, water), and compound *IIIc* (R = $COCH_3$) the product with m.p. 117—119°C, $[\alpha]_D^{20}$ −10·6° (*c* 6·20, water). Literature[21] gives for (*S*)-(−)-N-acetylalanine m.p. 122—123°C, $[\alpha]_D^{20}$ −62° (water).

Asymmetric Transformation of the Secondary Amines *IIa*—*IIc* (R = CH_3)

1 g (6·67 mmol) of (*S*)-(+)-hydratropic acid, $[\alpha]_D^{20}$ +86·6° (*in substantia*), in 1·5 ml of tetrahydrofuran was treated with a solution of 1·37 g (6·67 mmol) of dicyclohexylcarbodiimide in 4 ml of tetrahydrofuran. After standing for one hour, the solution of the acylating agent was cooled to −60°C and then mixed with 10 mmol of the racemic amine, *IIa*, *IIb* and *c*, respectively (R = = CH_3) in 10 ml of tetrahydrofuran. The mixture was allowed to stand at this temperature for one hour and then left at room temperature overnight. The deposited dicyclohexylurea was collected with suction and washed with ether. From the solution the unreacted amine was taken up in 2M-HCl and subsequently liberated with aqueous KOH. After extracting with ether and drying over KOH, the following amines were isolated: *IIIa* (R = CH_3), $[\alpha]_D^{20}$ −5·0° (ethanol), *IIIb* (R = CH_3), $[\alpha]_D^{20}$ −8·6° (ethanol), and *IIIc* (R = CH_3), respectively, $[\alpha]_D^{20}$ −6·2° (ethanol).

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