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STEREOCHEMISTRY AND PRODUCTS OF ADDITION OF TERT-BUTYLISONITRILE AT THE CARBONYL GROUP OF 3-HYDROXYPIPERIDIN-4-ONES

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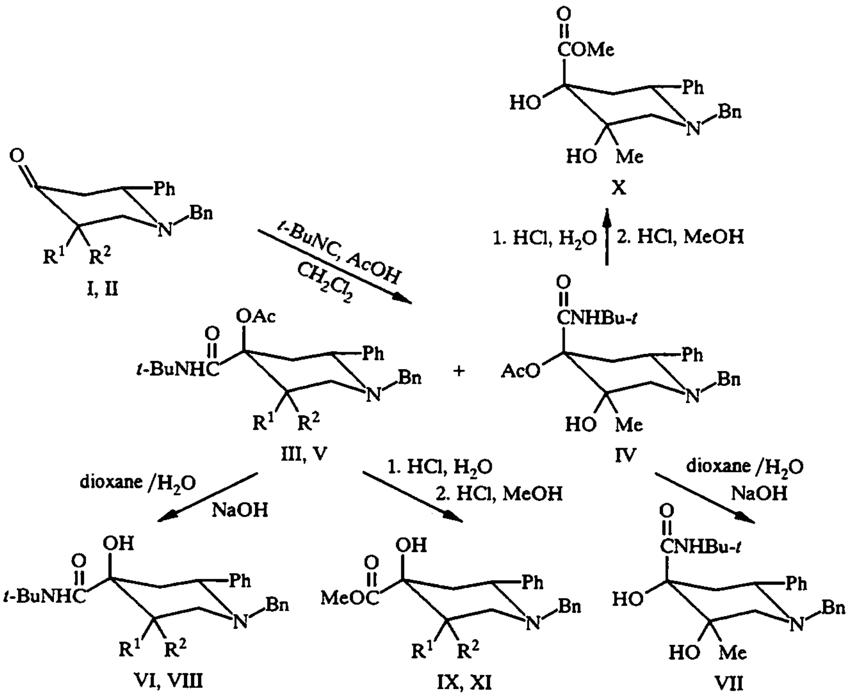
The stereochemistry and products of addition of tert-butylisonitrile at the carbonyl group of 3-hydroxypiperidin-4-ones have been studied. A preparative method for synthesis of 3-hydroxyisonipecotic acid derivatives has been developed. The orientation of the carbon containing substituent on the quaternary carbon atom was shown using ^{13}C *NMR vicinal* $^3J_{C,H}$ *spin couplings.*

A three component addition reaction of isonitriles at the double bond of ketones (known as the Passerini reaction) is a powerful method for the synthesis of α-hydroxycarboxylic acids [1-4]. However, the stereochemistry of addition of isonitriles at the carbonyl group of cyclic ketones has not been studied so far. In this work we have studied the stereochemistry and products of addition of tert-butylisonitrile to 3-hydroxypiperidin-4-ones I, II with the aim of synthesizing hydroxyisonipecotic acids which, depending on the relative configuration of the piperidine ring substituent, are agonists or inhibitors of γ-aminobutyric acid uptake [5]. We have shown that addition of tert-butylisonitrile to I and II occurs selectively to form the diastereomeric acylated amides III-V.



I, III, VI, IX R^1 = OH, R^2 = Me; II, V, VIII, XI R^1 = Me, R^2 = OH; Bn = CH_2Ph

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TABLE 1. Physicochemical Parameters for III-XI

Compound	^1H NMR spectrum												IR spectrum, ν, cm^{-1}
	chemical shift, δ, ppm									spin–spin coupling, J, Hz			
	t-Bu	3-CH_3	Ac	OCH_3	$^aH_6$	$^aH_5$	$^eH_5$	H_2	H_2	$^aH_5{}^aH_6$	$^eH_5{}^aH_6$	$^aH_5{}^eH_5$	
III	1,35	1,95	2,00	—	3,66	2,46	1,86	3,38	2,62	11,5	3,0	14,5	3560, 3420, 3300, 1740, 1680
IV	1,38	1,56	2,07	—	3,69	1,86	2,87	2,77	2,43	12,0	3,5	13,5	3480, 3420, 1740, 1720, 1680
V	1,34	1,16	2,18	—	3,38	2,22	3,21	2,60	2,60	11,5	3,0	15,0	3420, 3350, 1740, 1690
VI	1,34	1,38	—	—	3,51	2,42	2,72	2,52	2,37	12,0	3,5	14,0	3600, 3510, 3400, 1665
VII	1,38	1,46	—	—	4,06	1,80	2,03	2,82	2,52	12,0	3,5	13,5	3400, 3370, 1660
VIII	1,34	0,98	—	—	3,60	2,34	1,58	2,51	2,49	11,5	3,0	14,5	3320, 1660
IX	—	1,34	—	3,72	3,53	2,37	1,83	2,55	2,44	12,0	3,5	15,0	3610, 3500, 1740
X	—	1,44	—	3,81	3,91	1,83	1,88	2,66	2,53	11,5	4,0	14,0	3580, 3550, 1730
XI	—	1,09	—	3,72	3,54	2,67	1,73	2,52	2,52	11,5	3,0	14,5	3530, 1740

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*^1H NMR Spectra of III-V recorded using $CDCl_3$, VI-XI in CD_3OD.

TABLE 2. ^{13}C NMR Spectra of IX-XI in CD_3OD

Compound	Chemical shift, δ, ppm,								Spin–spin coupling, J, Hz	
	C_2, t	C_3, s	C_4, s	C_5, t	C_6, d	3-CH_3	OCH_3, q	CO	CO—$^aH_5$	CO—$^eH_5$
IX	59,10	77,24	71,07	41,73	62,56	23,33	51,30	173,26	<2,5	<2,5
X	59,19	78,45	72,47	44,27	64,61	22,89	51,49	174,49	6,5	3,3
XI	59,22	76,32	70,85	40,73	62,36	21,24	51,40	173,82	<2,5	<2,5

TABLE 3. Elemental Analytical Data for III-XI

Compound	Empirical formula	Found, % · Calculated, % C	H	N	mp, °C	Yield, %
III	$C_{26}H_{34}N_2O_4$	71.02 71,21	7.70 7,81	6.20 6,39	242...243	67,4
IV	$C_{26}H_{34}N_2O_4$	70.98 71,21	7.69 7,81	6.21 6,39	103...104	23,6
V	$C_{26}H_{34}N_2O_4$	71.09 71,21	7.72 7,81	6.24 6,39	148...149	92,0
VI	$C_{24}H_{32}N_2O_3$	72.54 72,70	8.07 8,13	6.94 7,06	197...198	93,0
VII	$C_{24}H_{32}N_2O_3$	72.49 72,70	7.99 8,13	6.89 7,06	165...166	95,0
VIII	$C_{24}H_{32}N_2O_3$	72.52 72,70	8.04 8,13	6.90 7,06	152...153	93,0
IX	$C_{21}H_{25}NO_4$	70.75 70,96	6.96 7,09	3.85 3,94	130...131	86,0
X	$C_{21}H_{25}NO_4$	70.69 70,96	6.92 7,09	3.78 3,94	148...149	87,0
XI	$C_{21}H_{25}NO_4$	70.82 70,96	7.01 7,09	3.86 3,94	113...115	90,0

Reaction of piperidone I with the isonitrile and acetic acid in dichloromethane gives a mixture of amides III and IV with a predominance of equatorial attack of the reagent at the carbonyl group (75/25) and with overall yield of 91%. In the case of the piperidone II, only the product with an equatorial orientation of the amide group (compound V) could be isolated in a yield of 92%. Hydrolysis of the acetate in basic aqueous-dioxane solution gives the diastereomeric dihydroxyamides VI-VIII in 93-95% yield. Hydrolysis of the acylated amides in concentrated hydrochloric acid and subsequent esterification with methanol gives the corresponding esters IX-XI in 86-90% yield.

Identification of compounds III-XI in their pure state was carried out using IR, ^{13}C and ^1H NMR spectroscopy (Tables 1 and 2). Thus in the ^1H NMR spectra of III-XI the proton signals for C_5 and C_6 were observed as three quadruplets and for C_2 as two doublets or an unresolved AB system with constants pointing to a chair like conformation of the piperidine ring [6].

The IR spectra of dilute solutions of the amides and esters are characterized by amide, acetyl, and ester carbonyl absorption bands at 1660-1690, 1720-1740, and 1730-1750 cm^{-1} respectively.

The configuration of the substituent at C_4 in the esters IX-XI was determined from ^{13}C NMR spectroscopic data using a previously developed method [7]. The carbon atoms signals for the compounds discussed occurred in the expected regions (Table 2). The signal for the carbonyl group carbon atom in CD_3OD with selective irradiation of the ester group protons depended only on its interaction through three bonds to the hydrogen atoms at C_5 since C_3 and C_4 are quaternary. It is known that the value of the vicinal spin-spin coupling between the ^{13}C and ^1H atoms depends on their dihedral angles and is similar to the Karplus relationship for protons [8]. Compounds IX-XI exist in one chair-like conformation differing only in the orientation at C_4. It is apparent that the spin-spin coupling value $^3J_{CO,aH}$ in the ^{13}C NMR of esters with an axial carbonyl group must be larger that the corresponding value for those with an equatorial carbonyl function.

The carbomethoxy carbonyl carbon in ester X appears as a double doublet with observed splitting of 3.0 and 6.5 Hz. Calculation of spectral parameters using the program PANIC and fitting into a standard mathematical instrumental set has shown that these values correspond to the spin-spin couplings $^3J_{aCO,eH5}$ and $^3J_{aCO,aH5}$ respectively within experimental accuracy. The carbonyl carbon signal in esters IX, XI is a broadened singlet with a half width of 2.5 Hz. The reported values for $^3J_{CO,H}$ point to an axial orientation of the carbomethoxy group in ester X and an equatorial one in IX, XI.

Hence a study of the Passerini reaction of 3-hydroxypiperidin-4-ones shows that tert-butylisonitrile attacks the carbonyl group carbon atom principally from the equatorial region and the approach reported is an extremely efficient method for synthesizing isonipecotic acid derivatives.

EXPERIMENTAL

^{1}H NMR Spectra for solutions in CD_3OD and $CDCl_3$ were obtained on Bruker AC-200 spectrometer with a working frequency of 200 MHz for the ^{1}H nucleus. ^{13}C NMR Spectra for solutions of IX-XI in CD_3OD were recorded on a Bruker AC-200 working at 50 MHz for the ^{13}C nucleus. Along with scanning spectra with full decoupling and without decoupling from protons, esters IX-XI were recorded over a narrow digital range (containing the carbonyl group carbon atom signal) in order to increase digital resolution (in this case 0.3 Hz). IR Spectra were recorded for solutions of III-XI in CCl_4 (10^{-3} molar) using a Specord-75IP spectrometer. Monitoring of the reaction and of product purity was carried out on Kieselgel TLC plates.

Elemental analytical data agreed with that calculated.

4a-Acetoxy-1e-benzyl-3e-hydroxy-3a-methyl-6e-phenylpiperidine-4e-(N-tert-butylcarboxamide) (III, $C_{26}H_{34}N_2O_4$) and 4e-Acetoxy-1e-benzyl-3e-hydroxy-3a-methyl-6e-phenylpiperidine-4a-(N-tert-butylcarboxamide) (IV, $C_{26}H_{34}N_2O_4$). Piperidone I (2 g, 6.8 mmole) was dissolved in dichloromethane (12 ml) at room temperature and tert-butylisonitrile (1.5 ml, 13.3 mmole) and glacial acetic acid (1.5 ml, 26.2 mmole) were added. After 3 h the solvent and reagents were distilled at reduced pressure and the residue was dissolved with heating in toluene (10 ml). Crystallization from toluene at −15°C gave the acylated amide III (2.0 g). Crystallization of the residue from a mixture of hexane and ether gave amide IV (0.7 g). The quantitative ratio of products, calculated by comparison of the ^{1}H NMR intensities of the methyl signals in the epimeric amides III and IV, was 75:25.

4a-Acetoxy-1e-benzyl-3a-hydroxy-3e-methyl-6e-phenylpiperidine-4e-(N-tert-butylcarboxamide)(V, $C_{26}H_{34}N_2O_4$) was prepared similarly from piperidone II.

1e-Benzyl-3e,4a-dihydroxy-3a-methyl-6e-phenylpiperidine-4e-(N-tert-butylcarboxamide) (VI, $C_{24}H_{32}N_2O_3$). Acylated amide III (0.5 g, 1.1 mmole) was dissolved with heating in a mixture of dioxane (20 ml) and water (8 ml) containing NaOH (0.3 g) and refluxed with a condenser for 4 h. The reaction mixture was then diluted with water (30 ml) and the crystals separated on the filter.

1e-Benzyl-3e,4e-dihydroxy-3a-methyl-6e-phenylpiperidine-4a-(N-tert-butylcarboxamide) (VII, $C_{24}H_{32}N_2O_3$) and 1e-benzyl-3a,4a-dihydroxy-3e-methyl-6a-phenylpiperidine-4e-(N-tert-butylcarboxamide) (VIII, $C_{24}H_{32}N_2O_3$) were prepared similarly.

Methyl 1e-Benzyl-3e,4a-dihydroxy-3a-methyl-6a-phenylpiperidine-4a-carboxylate (IX, $C_{21}H_{25}NO_4$). Amide III (1 g, 2.5 mmole) was dissolved in concentrated hydrochloric acid (25 ml) and refluxed with a condenser until disappearance of the starting amide. The reaction mixture was evaporated under reduced pressure and the hydrochloride residue was dissolved in dry methanol (20 ml) saturated with hydrogen chloride. At the end of the reaction the solvent was distilled off to dryness under reduced pressure and the hydrochloride dissolved in water and basified with sodium bicarbonate solution. The free base of IX was extracted with ethyl acetate and, after distillation of solvent, crystallized from a mixture of ethyl acetate and hexane.

Methyl 1e-benzyl-3e,4e-dihydroxy-3a-methyl-6e-phenylpiperidine-4a-carboxylate (X, $C_{21}H_{25}NO_4$) and 1e-benzyl-3a,4a-dihydroxyl-3e-methyl-6e-phenylpiperidine-4e-carboxylate (XI, $C_{21}H_{25}NO_4$) were prepared similarly.

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