DIASTEREOSELECTIVE METHYLATION OF 1s-α-PHENYLETHYL-$\Delta^{9,10}$-OCTAHYDROQUINOL-4-ONE[*]

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The methylation of the lithium derivative of 1s-α-phenylethyl-$\Delta^{9,10}$-octahydroquinol-4-one under kinetic-control conditions at −70°C in hexane is highly diastereoselective and leads to (+)-1s-α-phenylethyl-3-methyl-$\Delta^{9,10}$-octahydroquinol-4-one in 90% optical yield.

The fundamental possibility of the asymmetric electrophilic substitution of $\Delta^{9,10}$-octahydroquinol-4-one derivatives has been previously established. It has been shown [2] that the metallation of 1s-α-phenylethyl-$\Delta^{9,10}$-octahydroquinol-4-one (I) with a threefold excess of lithium diethylamide at −5°C in tetrahydrofuran (THF) and subsequent methylation with methyl iodide lead to the formation of a mixture of diastereomers of 3-methyl-substituted enamino ketone II and provide evidence that asymmetric electrophilic substitution proceeds in 42% optical yield. Consequently, a new chiral center develops in the 3 position of the quinolone system of enamino ketone I as a result of 1,4-asymmetric induction; the fixed s configuration of the asymmetric carbon atom of the α-phenylethyl substituent facilitates the formation of unequal amounts of only one pair of diastereomers of 1s-α-phenylethyl-3-methyl-$\Delta^{9,10}$-octahydroquinol-4-one (II).

To elucidate the factors that could lead to an increase in the optical yield of the reaction we made a detailed study of the methylation of the lithium derivative of enamino ketone I with methyl iodide under various conditions. We have also previously established [1] that, depending on the reaction conditions, the electrophilic substitution of 1-benzyl-$\Delta^{9,10}$-octahydroquinol-4-one (III) may take place in the 3 or 8 position of the quinolone system. We assumed that substitution in the 3 position can occur under kinetic-control conditions, whereas substitution in the 8 position is thermodynamically controlled. To shed some light on this question we studied the methylation of the lithium salt of 1-benzyl-$\Delta^{9,10}$-octahydroquinol-4-one (III) with methyl iodide under various conditions. The presence of only 3-methyl-substituted enamino ketone III was established chromatographically[†] in the metallation of enamino ketone III with a twofold excess of lithium diisopropylamide at 0°C for 1 h with subsequent methylation of a sample of the reaction mixture with methyl iodide. The lithium salt of enamino ketone III was then heated to 40°C and maintained at this temperature for 2 h. The formation of approximately equal amounts of both the 3- (IV) and 8-substituted enamino ketone III was observed chromatographically after the addition of methyl iodide. This confirms that the metallation of enamino ketone III at low temperatures takes place under kinetic-control conditions, whereas two different types of aza enolates A and B are formed when the mixture is heated (thermodynamic control). We carried out the subsequent investigation of the asymmetric methylation of enamino ketone I under kinetic-control conditions, i.e., in the presence of a twofold excess of lithium amide at low temperatures; this procedure leads to the formation of only 3-substituted enamino ketone I. We found that the reaction temperature has a pronounced effect on the ratio of diastereomers II. The formation of the mixture of two diastereomers IIa, b in a ratio of 36:64 (28% optical yield) was observed in the chromatographic analysis of the reaction mixture formed by the action of two equivalents of methyl iodide on the lithium salt of enamino ketone I at 0°C in THF. The ratio of diastereomers IIa, b was estimated by the weight method after isolation with a column packed with silica gel or from PMR data. Different chemical shifts of the methyl groups in the 3 position and in the α-phenylethyl substituent appear in the PMR spectra of the individual diastereo-

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[*] Communication 2 in the series "Metallation of cis-enamino ketones." See [1] for Communication 1.

[†] The spray technique was used in this research.

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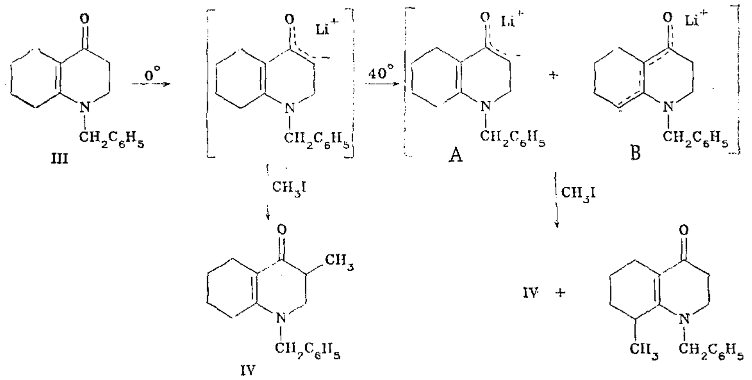
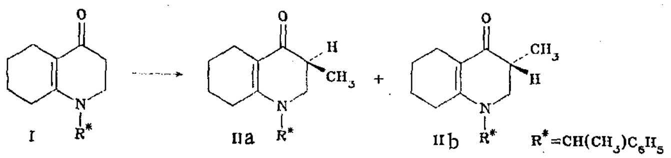


mers IIa, b; this also made it possible to estimate their diastereomeric purity, which was no less than 95%. An increase in the optical yield to 50 and 56%, respectively, was observed when the temperature was lowered to −15 and −30°C. Methylation of the lithium derivative of enamino ketone I in hexane—THF in a ratio of 2:1 led to the formation of diastereomers IIa, b in a ratio of 18:82 (64% optical yield). We were able to obtain the maximum optical yield in methylation by carrying out the reaction at −70°C in hexane—THF (10:1); the ratio of diastereomers IIa, b corresponded to an optical yield of 90%. Thus we found conditions for carrying out the methylation of the lithium salt of enamino ketone I with a high degree of diastereoselectivity. We then also established that the time and temperature of treatment of the reaction mixture with methyl iodide affect the ratio of diastereomers IIa, b. Thus when the reaction mixture after the addition of methyl iodide was stirred at −10°C for 30 min and then at 20°C for 3 h, a sample of the reaction mixture quenched with water contained a mixture of IIa, b in a ratio of 48:52. Decomposition of a sample of the same reaction mixture with concentrated hydrochloric acid led to an increase in the percentage of the primary formed diastereomer IIb in the mixture (the IIa, b ratio was 25:75); this may be associated with interconversion of diastereomers IIa, b as a result of epimerization in the 3 position of the quinolone system. In this connection, we evaluated the stabilities of individual diastereomers IIa, b in various media. The formation of a mixture of diastereomers IIa, b, in which starting isomer IIb predominated, was observed in the action of excess lithium amide on individual diastereomer IIb at 0°C with subsequent decomposition with water after 30 min; this confirms the possibility of epimeriaation of diastereomer IIb to IIa in the presence of a strong base in an aprotic medium. Only the conversion of isomer IIb to a mixture of IIa and IIb were refluxed in protic, aprotic, and strongly polar media for 10 h. It is presently difficult to ascertain the reason for precisely this tendency of the transformation; additional studies are necessary.



Thus we have shown that the methylation of 1-benzyl-$\Delta^{9,10}$-octahydroquinol-4-one under kinetic-control conditions proceeds regioselectively in the 3 position of the quinolone system. We found that the methylation of the lithium salt of 1s-α-phenylethyl-$\Delta^{9,10}$-octahydroquinol-4-one at −70°C in hexane is highly diastereoselective and leads to the formation of (+)-1s-α-phenylethyl-3-methyl-$\Delta^{9,10}$-octahydroquinol-4-one in 90% optical yield.

EXPERIMENTAL

The IR spectra of films and mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The UV spectra of solutions in methanol were obtained with a Cary-15 spectrophotometer. The PMR spectra of solutions in $CHCl_3$ were recorded with a T-60 spectrometer. The mass spectra were obtained with an MKh-1303 spectrometer. 1-Benzyl- (III) and 1-α-phenylethyl-$\Delta^{9,10}$-octahydroquinol-4-one (I) were obtained by the method in [3]; 1-benzyl-3-methyl-$\Delta^{9,10}$-octahydroquinol-4-one was obtained by the method in [2].

3-Methyl-1-α-phenylethyl-$\Delta^{9,10}$-octahydroquinol-4-one (IIa, b). A solution of 0.15 g (2 mmole) of (+)-1-α-phenylethyl-$\Delta^{9,10}$-octahydroquinol-4-one in 10 ml of THF was added dropwise in a stream of argon at −15°C to a solution of 4 mmole of lithium diethylamide in 4 ml of absolute THF [obtained from 2.95 ml of a 1.38 N solution of methyllithium in ether and 0.4 ml (4 mmole) of diethylamine]. After 40 min, 0.4 ml (6 mmole) of methyl iodide was added, and the mixture was stirred at −15°C for 30 min. It was then decomposed with water, the aqueous mixture was extracted with chloroform, and the extract was dried with Na_2SO_4. The solvent was removed, and the resulting brown oil (0.7 g) was applied to a column packed with silica gel by the dry method and eluted successively with benzene and benzene–acetone mixtures (8:1, 6:1, and 4:1). The chromatographically homogeneous fractions were evaporated to give 0.08 g (15%) of diastereomer IIa in the form of an oil with R_f 0.62 [Silufol, benzene–acetone (4:1)] $[\alpha]_D^{20}$ +246° (c 0.27, CH_3OH). IR spectrum (film): 1632 (conjugated CO) and 1557 cm^{-1} (conjugated C=C). UV spectrum (in heptane): λ_{max} 315 nm (ε 11,700); (in CH_3OH): λ_{max} 337 nm (ε 18,000). PMR spectrum ($CDCl_3$) 1.02 (3H, d, 3-CH_3), 1.58 (3H, d, CH_3 group of the α-phenylethyl substituent), and 7.13 ppm (5H, s, C_6H_5). Found: C 80.3; H 8.9%. $C_{18}H_{23}NO$. Calculated: C 80.3; H 8.6%] and 0.24 g (45%) of isomer IIb with R_f 0.59 [Silufol, benzene–acetone (4:1)] [$[\alpha]_D^{20}$ +142° (c 0.32, CH_3OH) and mp 71-72°C (from hexane). IR spectrum (mineral oil): 1620 (conjugated CO) and 1560 cm^{-1} (conjugated C=C). UV spectrum (in heptane): λ_{max} 316 nm (ε 15,400); (in CH_3OH): 338 nm (ε 21,000). PMR spectrum ($CDCl_3$): 0.91 (3H, d, 3-CH_3), 1.63 (3H, d, CH_3 group of the α-phenylethyl substituent), 5.21 (1H, q, phenylethyl CH), and 7.12 ppm (5H, s, C_6H_5). Found: C 80.4; H 8.9%. $C_{18}H_{23}NO$. Calculated: C 80.3; H 8.6%].

Variation of the Conditions for Methylation of Enamino Ketone I That Affect the Ratio of Diastereomers IIa, b. 1. A solution of 0.26 g (1 mmole) of enamino ketone I in 10 ml of THF was added dropwise at 0°C in a stream of argon to a solution of 2 mmole of lithium diisopropylamide in 4 ml of absolute THF [obtained from 1.54 ml of a 1.4 N solution of methyl lithium in ether and 0.28 ml (2 mmole) of diisopropylamine]. After 30 min, 0.2 ml (3 mmole) of methyl iodide was added, and the mixture was stirred at 0°C for 30 min. The mixture was decomposed with water and extracted with chloroform, and the extract was dried with Na_2SO_4. Removal of the solvent gave 0.76 g of a brown oil, which was applied to a columm packed with silica gel by the dry method and eluted successively with benzene and benzene–acetone mixtures (10:1, 8:1, and 6:1). The chromatographically homogeneous fractions were evaporated to give 0.07 g (24%) of diastereomer IIa and 0.12 g (45%) of diastereomer IIb in a ratio of 36:64.

2. A solution of 1.04 g (4 mmole) of enamino ketone I in 20 ml of THF was added dropwise in a stream of argon at −15°C to a solution of 8 mmole of lithium diethylamide in 10 ml of absolute THF. After 40 min, 0.8 ml (12 mmole) of CH_3I was added, and the mixture was stirred at −15 °C for 1 h and at room temperature for 3 h. It was then decomposed with water at 0°C, the aqueous mixture was extracted with chloroform, and the extract was dried with Na_2SO_4. Chromatographic separation was described in the preceding experiment gave 0.3 g (28%) of diastereomer IIa and 0.33 g (30%) of diastereomer IIb in a ratio of 48:52.

3. A similar reaction with decomposition of the reaction mixture with concentrated hydrochloric acid at 0°C and chromatographic separation with a column packed with silica gel by successive elution with benzene and benzene–acetone mixtures (10:1, 6:1, and 4:1) gave 0.18 g (16%) of isomer IIa and 0.54 g (50%) of isomer IIb in a ratio of 25:75.

4. A solution of 0.51 g (2 mmole) of enamino ketone I in 10 ml of THF was added dropwise in a stream of argon at −30°C to a solution of 4 mmole of lithium diisopropylamide in 10 ml of absolute THF. After 40 min, 0.4 ml (6 mmole) of CH_3I was added, and the mixture was stirred at −30°C for 30 min. It was then decomposed with water, the aqueous mixture was extracted with chloroform, and the extract was dried with Na_2SO_4. Chromatographic separation with a column gave 0.08 g (14%) of diastereomer IIa and 0.35 g (66%) of diastereomer IIb in a ratio of 22:78.

5. A solution of 0.51 g (2 mmole) of enamino ketone I in 2 ml of THF was added dropwise in a stream of argon at −70°C to a solution of 4 mmole of lithium diisopropylamide in 13 ml of absolute hexane and 5 ml of THF [obtained from a 0.95 N solution of butyllithium in hexane and 0.56 ml (4 mmole) of diisopropylamine]. After 1 h, 0.4 ml (6 mmole) of CH_3I was added, and the solution was stirred at −70°C for 30 min. It was then decomposed with water and worked up in the usual way to give 0.07 g (10%) of diastereomer IIa and 0.28 g (57%) of diastereomer IIb in a ratio of 18:82.

6. A solution of 0.51 g (2 mmole) of enamino ketone I in 2 ml of THF was added dropwise in a stream of argon at −70°C to a solution of 4 mmole of lithium diisopropylamide in 20 ml of absolute hexane. After 1 h at the same temperature, 0.4 ml (6 mmole) of CH_3I was added,

and the solution was stirred at −70°C for 30 min. It was then decomposed with water and worked up in the usual way to give 0.03 g (3%) of diastereomer IIa and 0.29 g (57%) of diastereomer IIb in a ratio of 5:95.

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C- AND N-ALKYLATION OF 4,5-DIHYDRO-1H-INDENO[1,2-b]PYRIDINE DERIVATIVES

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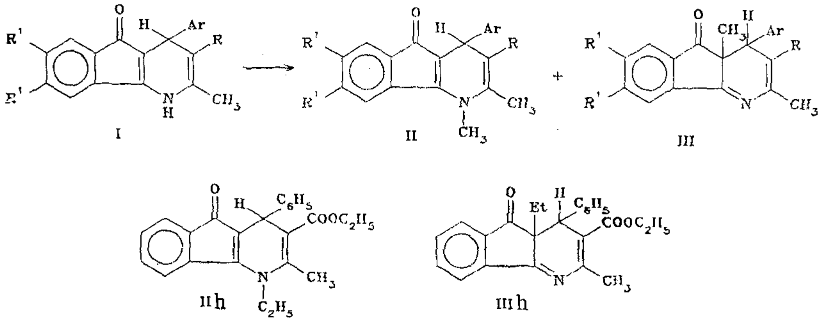
2-Methyl-4-aryl-5-oxo-4,5-dihydro-1H-indeno[1,2-b]pyridine derivatives react with methyl iodide in an aprotic medium in the presence of alkaline agents to give C- and N-alkylation products, viz., 2,4a-dimethyl- and 1,2-dimethyl-4-aryl-5-oxo-4,5-dihydroindeno[1,2-b]pyridines, and with dimethyl sulfate or methyl p-tosylate under the same conditions to give N-methylation products.

1,4-Dihydropyridine derivatives that contain electron-acceptor substituents attached to the $C_{(3)}$ and $C_{(5)}$ atoms and 5-oxo-4,5-dihydroindeno[1,2-b]pyridines are conjugated enamino ketone systems (from the IR spectra [1, 2] and their acidic properties [3]); however, the characteristic chemical properties of these systems have not yet been observed. Aminovinyl ketones of the indene series can be alkylated at one of three centers, viz., O, N, or C, depending on the conditions [4]; however, only N-alkyl derivatives are formed in the alkylation of 3,5-diethoxycarbonyl- [5] and 3,5-diacetyl-1,4-dihydropyridines [6] or 5-oxo-3-alkylthiocarbonyl-4,5-dihydroindeno[1,2-b]pyridine derivatives [3].

We have shown that 4,5-dihydro-1H-indeno[1,2-b]pyridine derivatives (I) in the presence of alkaline agents, i.e., in the anionic form, react with dimethyl sulfate or methyl p-toluenesulfonate to give exclusively N-methyl derivatives II, whereas their dual reactivity is manifested in the reaction with alkyl iodides, and mixtures of N- (II) and C-alkylation (III) products are formed.



I—III a R=COOC$_2$H$_5$, Ar=C$_6$H$_5$, R'=H; b R=COCH$_3$, Ar=C$_6$H$_5$, R'=H; c R=CN, Ar=C$_6$H$_5$, R'=H; d R=R'=H, Ar=C$_6$H$_5$; e R=COOC$_2$H$_5$, Ar=C$_6$H$_4$NO$_2$-4, R'=H; f R=COOC$_2$H$_5$, Ar=C$_6$H$_4$OCH$_3$-4, R'=H; g R=COOC$_2$H$_5$, Ar=C$_6$H$_5$, R'=Cl

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