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STEREOCHEMISTRY OF THE ASYMMETRIC ALKYLATION OF $\Delta^{9,10}$-OCTAHYDROQUINOLIN-4-ONES

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The asymmetric character of the alkylation of a series of metallated bicyclic enaminoketones has been established and its stereoselectivity has been investigated. The enantiomers of (3S)-methyl- and (3S*)- and (3R*)-3-methyl-3'-butyl-$\Delta^{9,10}$-octahydroquinolin-4-ones have been obtained. The possibility of inducing chirality at the 3 position of the enaminoketone molecule during methylation in the presence of chiral lithium amides has been established in principle.*

Chiral bicyclic cis-enaminoketones (EAK) are simple and convenient models for obtaining biologically active derivatives of octa- and decahydroquinoline, the structural basis of a series of alkaloids, azasteriods, and neurotoxins. The present communication† is an investigation of the diastereoselectivity of the alkylation of the metallated $\Delta^{9,10}$-octahydroquinolin-4-ones (I)-(III) and its dependence on the nature of the alkylating agent and the chiral substituent at the nitrogen atom. Study of the chiroptical properties of the individual diastereomers of 3-alkyl substituted enaminoketones enabled a true picture of the competing influences of kinetic and thermodynamic factors on the alkylation process to be established. It was also shown possible to effect asymmetric induction on metallating the racemic enaminoketone (I) in the presence of chiral lithium amides.

We previously showed the possibility of carrying out electrophilic substitution of $\Delta^{9,10}$-octahydroquinolin-4-ones [1, 2]. Optimum conditions were found for kinetic control in which a high selectivity was achieved for the metallation of the lithium salt of 1-(S-α-phenylethyl)-$\Delta^{9,10}$-octahydroquinolin-4-one (I). Conditions were −70°C in a hexane–tetrahydrofuran (THF) mixture (10:1), giving 100% regioselectivity and 90% optical yield of (+)-1-(S-α-phenylethyl)-3-methyl-$\Delta^{9,10}$-octahydroquinolin-4-one (IVb) with a lower chromatographic mobility. A new stereogenic center arises at position 3 of the quinolone system of the enaminoketone (IV) as a result of 1,4 asymmetric induction. We linked the appearance of the minor isomer (+) (IVa) in the reaction mixture with the thermodynamic instability of the predominant diastereomer (+) (IVb), which epimerizes readily at position 3 of the quinolone system.

We investigated the diastereoselectivity of the alkylation of the series of $\Delta^{9,10}$-octahydroquinolin-4-ones (I)-(III) containing various chiral substituents of the (S) configuration at the nitrogen atom, widening the range of alkylating agents in order to clarify the steric course of the asymmetric alkylation of metallated enaminoketones.

The structures of the individual diastereomers (IVa,b)-(IXa,b), which were isolated by column chromatography, were confirmed by data of spectral and elemental analysis, and by mass spectrometry. The properties of the diastereoisomers of the 3-alkyl substituted enaminoketones (IVa,b)-(VIIIa,b) are given in Table 1.

Both the nature of the alkylating agent and the character of the chiral substituent at the nitrogen atom exert a profound effect on the diastereoselectivity of the alkylation of metallated enaminoketones (Table 2). In all cases the diastereomer b with a lower chromatographic mobility predominated. However the diastereoselectivity was reduced on increasing the bulk of the alkylating agent. Methylation of enaminoketones (II) and (III), having chiral α-benzylethyl and sec-butyl substituents of the (S) configuration at the nitrogen atom, was also accompanied by a reduction in diastereoselectivity, and consequently led to the formation of diastereomers of the 3-methyl substituted enaminoketones (VIIIa,b) and (IXa,b) in ratios of 35:65 and 50:50 respectively.

†This communication is part of the report "Stereoselective synthesis of piperidine derivatives" presented at an interinstitute colloquium, Chernogolovka, 1995.

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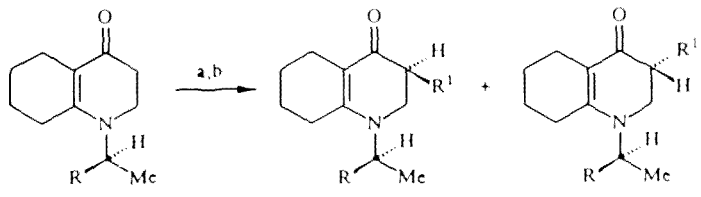
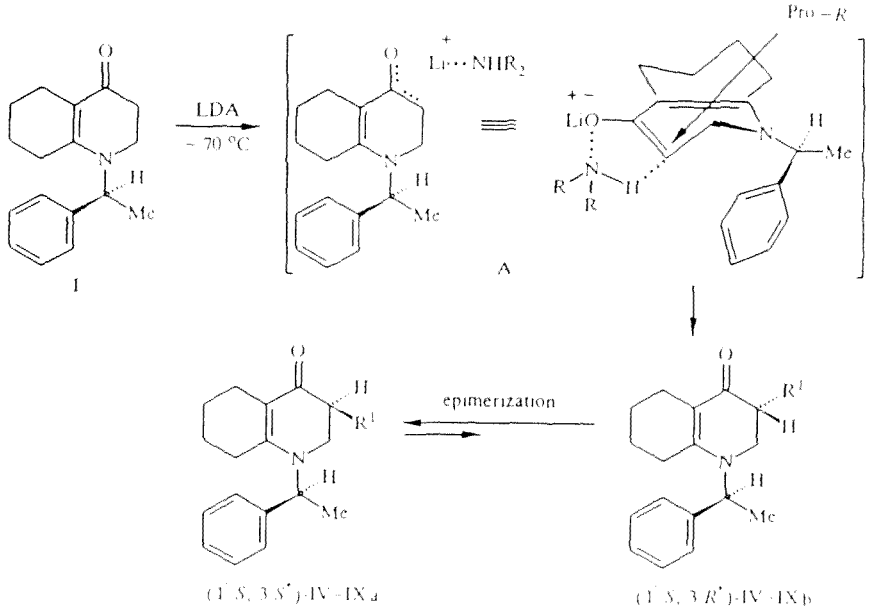


I R = Ph; II R = CH_2Ph; III R = CH_2Me; IV R = Ph, R^1 = Me; V R = Ph, R^1 = CH_2Me; VI R = Ph, R^1 = $CHMe_2$; VII R = Ph, R^1 = CH_2Ph; VIII R = CH_2Ph, R^1 = Me; IX R = CH_2Me, R^1 = Me
Reagents and conditions: a — LDA (2 eq), -15 °C, THF; b — R^1X

In reality the results shown in Table 2 reflect the asymmetric character of the alkylation of the metallated bicyclic enaminoketones (I)-(III). However, as was shown previously [2], to achieve high diastereoselectivity in each particular case requires careful optimization of the alkylation conditions is in addition to a reliable assessment of the thermodynamic stability of the diastereomers of the 3-alkyl substituted enaminoketones (IVa,b)-(IXa,b).

From these data the steric course of the asymmetric alkylation of metallated enaminoketones becomes clear. Under the action of a strong base the kinetically controlled monodeprotonation of enaminoketone (I) at position 3 leads to the formation of the corresponding enolate A, existing in the form of a tight ion pair with the lithium cation. The conformational rigidity of this enolate A is explained by coordination with diisopropylamine. This in its turn leads to differentiation between the prochiral sides of the $C_{(3)}=C_{(4)}$ bond. Attack of alkyl halide occurs preferentially on the sterically unhindered pro-(R) side. Consequently it is possible to predict the generation of a new chiral center at $C_{(3)}$ with the R configuration in the predominant diastereomer.

In other words, in the asymmetric alkylation of enaminoketone (I) by various alkyl halides the diastereomer having (1′S, 3R*) configuration of the 3-alkyl substituted enaminoketones must be formed preferentially.



The chiroptical properties of the diastereomers of the 3-alkyl substituted enaminoketones (IVa,b)-(IXa,b) and of the enaminoketone (I) have been considered. In the circular dichroism (CD) curves of the diastereomeric 3-methyl-enaminoketones (IVa) and (IVb) and in the CD curve of enaminoketone (I) in heptane an intense positive cotton effect (CE) was observed at 320-330 nm corresponding to the $\pi-\pi^*$ transition of the enaminoketone chromophore (Fig. 1). These data are in good agreement with the data of UV spectra (Fig. 2). However a comparison of the course of the CD curves of the diastereomeric

TABLE 1. Properties of the Diastereomers of 3-Alkyl Substituted Enaminoketones (IVa,b)-(VIIa,b)

Compound		T_{mp}, °C	R_f*1	IR spectrum, ν, cm^{-1}		M+	$[\alpha]_D^{20}$ (conc.)	UV spectrum, nm (ε)		PMR spectrum, δ, ppm ($CDCl_3$)
				C=O	C=C			heptane	methanol	
IV	(1'S, 3S*)-a	–	0,62	1632*2	1557	269	+246 (0,27)	315 (16140)	337 (18000)	1,02 (3H, d, CH_3), 1,58 (3H, d, CH_3–CH–C $_6H_5$), 5,2 (1H, qv, CH_3–CH–C $_6H_5$), 7,21 (5H, s, CH_3–CH–C $_6H_5$)
	(1'S, 3R*)-b	71 73	0,59	1620*3	1560	269	+142 (0,32)	316 (15400)	338 (21000)	0,91 (3H, d, CH_3), 1,63 (3H, d, CH_3–CH–C $_6H_5$), 5,21 (1H, qv, CH_3–CH–C $_6H_5$), 7,21 (5H, s, CH_3–CH–C $_6H_5$)
V	(1'S, 3S*)-a	–	0,66	1630*2	1557	283	+251 (0,31)	312 (19700)	337 (10500)	0,85 (3H, t, CH_3–CH_2), 1,53 (3H, d, CH_3–CH–C $_6H_5$), 5,13 (1H, qv, CH_3–CH–C $_6H_5$), 7,23 (5H, s, CH_3–CH– C_6H_5)
	(1'S, 3R*)-b	89 90	0,59	1615*3	1550	283	+154 (0,63)	316 (11600)	340 (15900)	0,55 (3H, t, CH_3–CH_2), 1,53 (3H, d, CH_3–CH–C $_6H_5$), 5,13 (1H, qv, CH_3–CH–C $_6H_5$), 7,23 (5H, s, CH_3–CH– C_6H_5)
VI	(1'S, 3S*)-a	–	0,71	1634*2	1560	297	+233 (0,028)	317 (21400)	340 (17800)	0,79 and 0,90 (6H, 2d, CH_3–CH–CH_3), 1,53 (3H, d, CH_3–CH–C $_6H_5$), 5,18 (1H, qv, CH_3–CH–C $_6H_5$), 7,21 (5H, s, CH_3–CH–C $_6H_5$)
	(1'S, 3R*)-b	112 114	0,65	1630*3	1557	297	+333 (0,015)	316 (22400)	340 (24600)	0,65 and 0,87 (6H, 2d, CH_3–CH– CH_3), 1,55 (3H, d, CH_3–CH–C $_6H_5$), 5,18 (1H, qv, CH_3–CH–C $_6H_5$), 7,3 (5H, s, CH_3–CH–C $_6H_5$)
VII	(1'S, 3S*)-a	–	0,73	1630*2	1558	345	+303 (0,091)	320 (13800)	340 (11300)	1,31 (3H, d, CH_3–CH–C $_6H_5$), 4,97 (1H, qv, CH_3–CH–C_6H_5), 6,97 (5H, s, $C_6H_5CH_2$), 7,08 (5H, s, CH_3–CH–C $_6H_5$)
	(1'S, 3R*)-b	49 51	0,71	1630*3	1558	345	+128 (0,089)	318 (13000)	340 (15600)	1,34 (3H, d, CH_3–CH–C $_6H_5$), 5,07 (1H, qv, CH_3–CH–C_6H_5), 7,0 (5H, m, C_6H_5–CH_2), 7,02 (5H, m, CH_3–CH–C $_6H_5$)

*From heptane.

*1Silufol, benzene–acetone, 4:1.

*2Thin film.

*3In Nujol.

*4In methanol.

TABLE 2. Asymmetric Alkylation of the Enaminoketones (I)-(III) (−15°C, 2 eq. LDA, THF)

3-Alkyl-EAK	N−R*	3-R[1]	Ratio of diastereomers, a:b	Optical yield, %
IV	CH(Me)Ph	Me	25 : 75	50
V	CH(Me)Ph	CH_2Me	35 : 65	30
VI	CH(Me)Ph	$CHMe_2$	44 : 56	12
VII	CH(Me)Ph	CH_2Ph	48 : 52	4
VIII	$CH(Me)CH_2Ph$	Me	35 : 65	30
IX	$CH(Me)CH_2Me$	Me	50 : 50	0

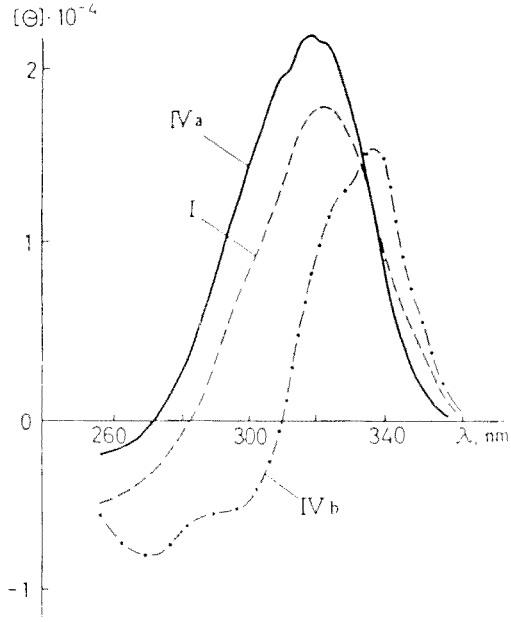
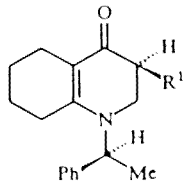


Fig. 1. CD curves of enaminoketones (1'S, 3S*) (IVa), (1'S, 3R*) (IVb), and (1'S) (I) in heptane.

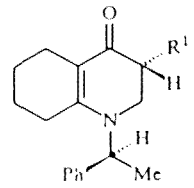
pair (IVa) and (IVb) with that of enaminoketone (I) showed that for the minor diastereomer (IVa) an increase was observed in the intensity of the CE of the $\pi-\pi^*$ transition and a decrease in intensity was observed for the predominating diastereomer (IVb). A similar pattern of the curves and regularity in the change of intensity of the $\pi-\pi^*$ band was also observed for each pair of diastereomers *a* and b for the whole series of 3-alkyl substituted enaminoketones (V)-(IX).

The emergence of a new chiral center of different configuration at position 3 of the enaminoketones (IVa, b)-(IXa, b) did not prove to have a significant effect on the enaminoketone chromophore, the positive sign of the CE of the $\pi-\pi^*$ transition was retained, and only its intensity was changed. This points to a stronger asymmetric disturbance of the enaminoketone chromophore by the chiral substituent at the nitrogen atom than by the asymmetric center at $C_{(3)}$. Consequently only the change in intensity of the CE of the $\pi-\pi^*$ transition of the enaminoketone chromophore observed for the diastereomers *a* and b reflects the contribution of the different chirality of the $C_{(3)}$ center to the overall rotation of the 3-alkyl substituted enaminoketone molecules (IV)-(IX).

It is accepted that the contributions to the overall rotation are summed if the chiral centers of the molecule have identical configurations. Then on calculating the contributions for the diastereomers of the 3-alkyl enaminoketones (IV)-(IX) having the (1'S, 3S*) configuration a strengthening might be expected in the intensity of the CE of the $\pi-\pi^*$ transition. For the (1'S, 3R*) diastereomers a weakening of the intensity compared with the enaminoketone (I) unsubstituted at position 3 would be expected. On this basis it may be proposed that the predominant diastereomers (IVb)-(IXb) probably have a 1'S, 3R*) configuration and the minor diastereomers (IVa)-(IXa) a (1'S, 3S*) configuration.



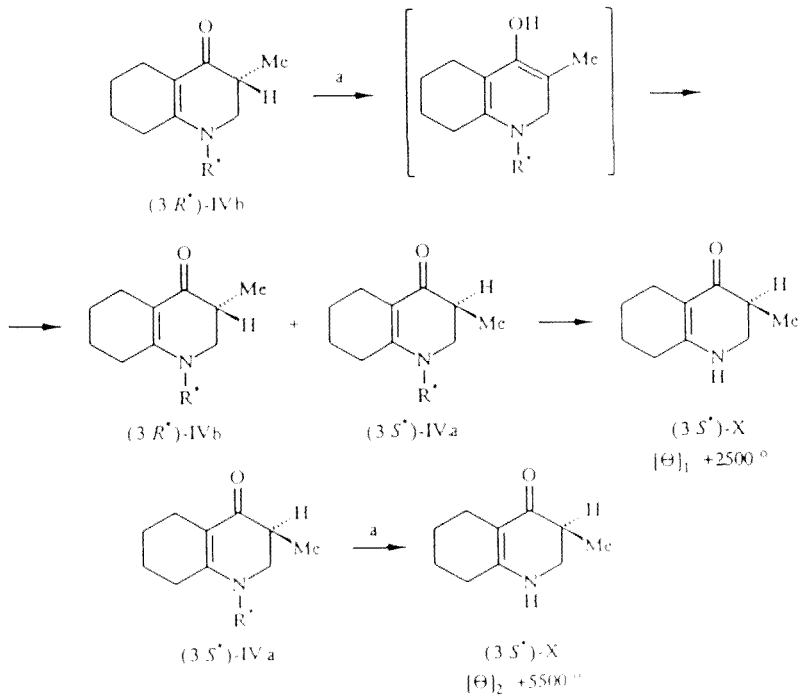
(1′*S*, 3*S*•) -IVa-IVa



(1′*S*, 3*R*•) -IVb-IVb

Thus consideration of the topology of the asymmetric alkylation of enaminoketone (I) and of the chiroptical data of the enaminoketones (IVa,b)-(IXa,b) leads to agreement with the stereochemical conclusions. On asymmetric alkylation of the metallated bicyclic enaminoketones (I) by various alkyl halides diastereomers of 3-alkyl substituted enaminoketones are formed in which the (3R•) configuration predominates at the new center.

Isolation of an enantiomer of enaminoketone (X) on removing the chiral tag from each of the individual diastereomers (1′S, 3S•) (IVa) and (1′S, 3R•) (IVb) by hydrogenolysis over palladium black is additional confirmation of the asymmetric character of the alkylation of enaminoketone (I). After hydrogenolysis only the (+)-enantiomer of 3-methyl-$\Delta^{9,10}$-octahydroquinolin-4-one (X) was obtained having differing optical purity and not the antipodes of enaminoketone (X) which might have been expected. A reduction in the size of the molecular ellipticity of the $\pi-\pi^*$ band in the (=) enantiomer of (X) obtained from (1′S, 3R•) enaminoketone (IVb) may be explained by the presence in it of (X) racemate. Consequently under the reaction conditions a partial epimerization of the (3R•) diastereomer (IVb) into the thermodynamically more stable (3S•) diastereomer (IVa) occurs initially and is followed by hydrogenolysis of the C–N bond.



(3*R*•)-IVb

(3*R*•)-IVb (3*S*•)-IVa (3*S*•)-X

$[\Theta]_1$ +2500°

(3*S*•)-IVa (3*S*•)-X

$[\Theta]_2$ +5500°

Reagents and conditions: R• = (*S*)-CH(Me)Ph, a) H_2, Pd, MeOH, 25°C, 3 h

The facile epimerization of the (1′S, 3R•) diastereomer (IVb) is caused by enolization of the carbonyl group of the enaminoketone occurring most rapidly of all with the participation of palladium black. In the absence of palladium, isomerization of (3R•) (IVb) to (3S•) (IVa) is observed only at the chromatographic level on boiling a methanol solution of (IVb) for 10 h. The analogous isomerization of (3S•) (IVa) to (3R•) (IVb) was not observed. It may therefore be proposed that the formation of the (1′S, 3R•) diastereomer (IVb) is kinetically controlled while the 1′S, 3S•) diastereomer (IVa) is thermodynamically the more stable.

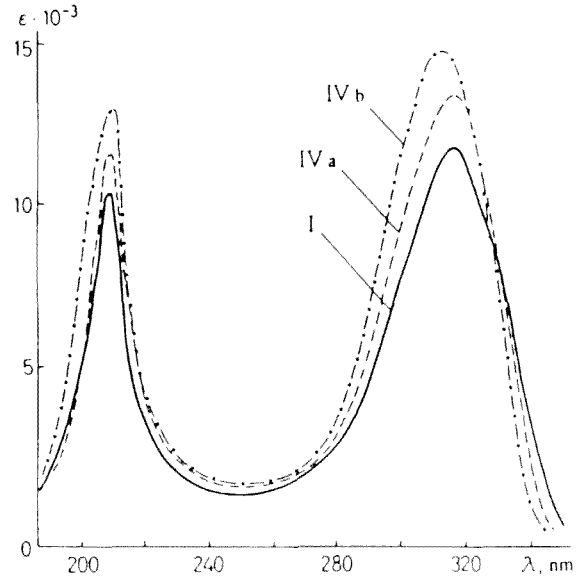


Fig. 2. UV spectra of enaminoketones (1'S, 3S*) (IVa), (1'S, 3R*) (IVb), and (1'S) in heptane.

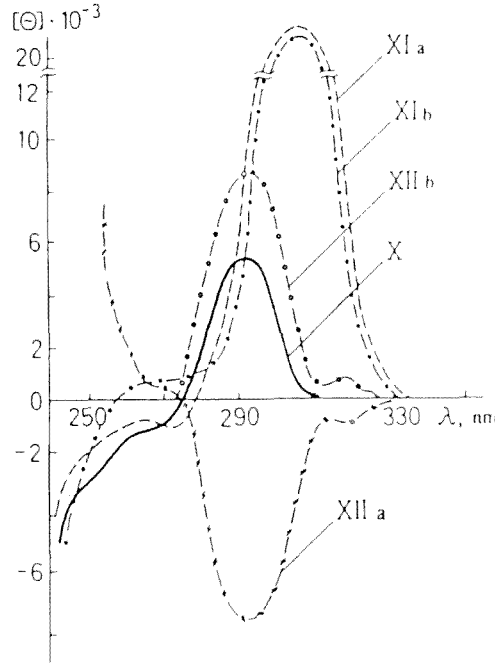
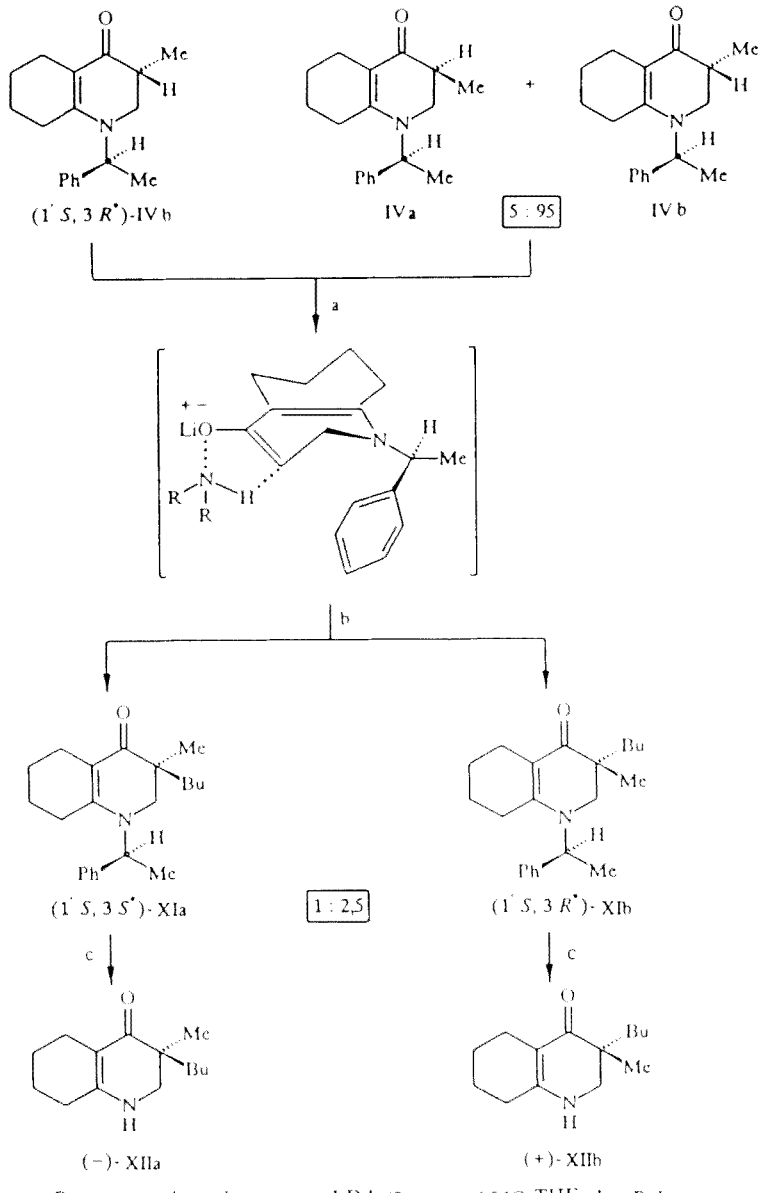


Fig. 3. CD curves of enaminoketones (1'S, 3S*) (XIa), (1'S, 3R*) (XIb), (−) (XIIa), (+) (XIIb), and (3S*) (X) in heptane.

In order to exclude the influence of epimerization at the $C_{(3)}$ atom in the diastereomers of 3-substituted enaminoketones on the true result of asymmetric alkylation, the enantiomers of 3-methyl-3'-butyl-$\Delta^{9,10}$-octahydroquinolin-4-one (XIIa, b) were prepared containing a quaternary carbon atom at position 3 of the quinolone system. For this purpose the diastereomers of 1-(S-α-phenylethyl)-3-methyl-3'-butyl-$\Delta^{9,10}$-octahydroquinolin-4-one (XIa) and (XIb) were obtained, in a 1:2.5 ratio, by the alkylation with butyl iodide of the lithium derivative of diastereomerically pure (1'S, 3R*) enaminoketone (IVb) or of a mixture of diastereomers (IVa):(IVb) of composition 5:95. In this case also the alkylation pattern established previously was retained. The predominant diastereomer has a lower chromatographic mobility and possibly the same (3R*) stereochemistry. Further, the chiral substituent was removed by hydrogenolysis from each of the diastereomers (XIa) and (XIb) and the (−) (XIIa) and

(+) (XIIb) enantiomers respectively of 3-methyl-3′-butyl-$\Delta^{9,10}$-octahydroquinolin-4-one were isolated. The opposite course of the CD curves and the practically identical values of $[\theta]$ confirmed their enantiomeric character (Fig. 3).



Reagents and conditions: a — LDA (2 eq.), -15 °C, THF; b — BuI; c — H_2, Pd, MeOH, 25 °C, 3 h

We assumed that on hydrogenolysis of the predominant diastereomer (XIb) belonging to the (3R*) series the (3R*) enantiomer of 3-methyl-3′-butyl-$\Delta^{9,10}$-octahydroquinolin-4-one, which is configurationally linked with it, is formed and consequently has a negative sign for the CE of the $\pi - \pi^*$ transition of the enaminoketone chromophore. The (3S*) enantiomer with a positive CE is formed from the minor diastereomer (XIa). However the result proved unexpectedly to be directly the opposite. On hydrogenolysis of the predominant diastereomer (XIb) the (+) enantiomer (XIIb) was obtained and the (−) enantiomer (XIIa) was formed from the minor diastereomer (XIa). A final answer to the stereochemical interrelationships in the series of chiral bicyclic enaminoketones (I)-(XII) may probably only be obtained by determining the absolute configuration of the diastereomers *a* and b by x-ray analysis and by a detailed analysis of the chiroptical properties of a large series of model enaminoketones.

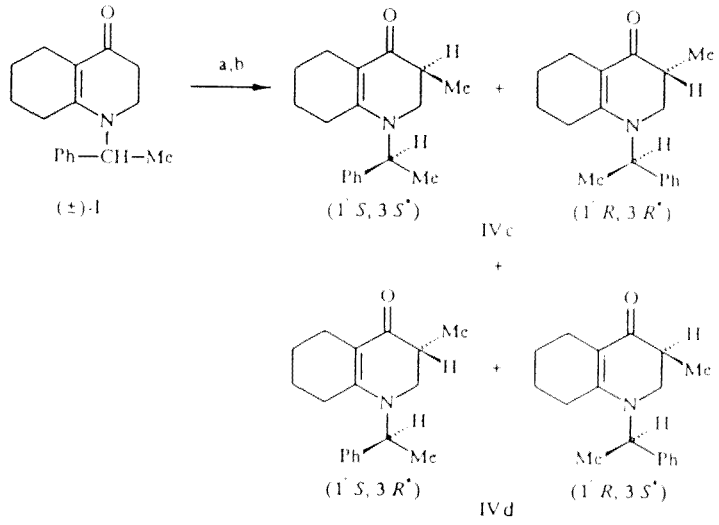
When studying the factors affecting the degree of diastereoselectivity of the alkylation of metallated enaminoketones the role of the secondary amine formed in the reaction medium from the lithium amide did not become clear until the end. We attempted to clarify whether in fact coordination exists between this amine and the lithium enolate A formed on metallation of the initial enaminoketone, as has been proposed previously. In order to answer this problem we carried out methylation of

TABLE 3. Values of the Specific Rotation of Diastereomer (IVd)

Isomer	$[\alpha]^{20}_D$ (concn. in methanol)	Optical purity, % (dominant configuration)	Chiral amine used to obtain lithium amide
(1'*S*, 3*R**)IVb	+142° (0,32)	>99	—
IVd	-15° (13)	10,5 (*R**)	(+)-(*R*)-MeNHCH(Me)Ph
IVd	+10° (10)	7,0 (*S**)	(-)-((*S*)-CH(Me)Ph)$_2$NH
IVd	+16° (9)	11,2 (*S**)	(-)-(S)-salsolidine

the racemic enaminoketone (I) in the presence of chiral lithium amides. (+)-N-Methyl-(R)-α-phenylethylamine [3], (−)-di-(S-phenylethyl)amine [4], and (−)-(S)-salsolidine were used to obtain chiral lithium amides. The predominant isomer (IVd), isolated by column chromatography, proved in all cases to be optically active. Values are given in Table 3 for the specific rotation of the diastereomer (IVd) obtained on using the three chiral lithium amides.

Can we understand these data? We recall that the sign of the CE of the $\pi-\pi^*$ transition in enaminoketones may be used to determine the absolute configuration of the primary chiral amines from which they were obtained. The sign of the CE of the $\pi-\pi^*$ transition is always positive for amines of the (S) configuration, and always negative for amines of the (R) series [5]. As was shown above this rule is also retained for chiral 3 substituted enaminoketones. Based on this the results given in Table 3 may be explained stereochemically in the following way. Theoretically four stereoisomers or two enantiomeric pairs (IVc) and (IVd), which is the same thing, may be formed by the methylation of racemic enaminoketone (I) in the presence of a chiral secondary amine. Some excess of one of the enantiomers of a pair over the corresponding racemate may be estimated from the size of the specific rotation of a sample reflecting its optical purity. The data of Table 3 describe precisely that result. A small excess of the (+)-(1'S, 3R*) enantiomer of (IVd) mixed with the corresponding racemate is formed in the presence of lithium amides synthesized from secondary amines of the (S) configuration, viz. (−)-salsolidine and (−)-di-(α-phenylethyl)amine, while the (−)-(1'R, 3S*)-enantiomer of (IVd) predominates when using N-methyl-α-phenylethylamine of the (R) configuration. The optical purity of the diastereomers of (IVd) obtained in all three experiments and estimated by comparing values of their specific rotation with that of optically pure (+)-(1'S, 3R*)-(IVb) proved to be low. Nonetheless these data are very interesting since they show in principle the possibility of obtaining optically active 3-alkyl substituted enaminoketones by alkylating in the presence of chiral lithium amides. In other words, induction of optical activity occurs in the process of forming a new C−C bond at position 3 of the enaminoketone (I) by transfer of chirality from the secondary amine to the newly generated chiral center at $C_{(3)}$. In our opinion the transfer of chirality occurs only when the chiral secondary amine is coordinated with the enolate A since only this leads to differentiation of the prochiral sides of the $C_{(3)}=C_{(4)}$ bond of the enolate.



Reagents and conditions: a — LDA (2 eq.), -15 °C, THF; b — MeI

Development of a strategy for the diastereoselective 1,4-hydride reduction of enaminoketones [6] and the subsequent or previous alkylation of chiral bicyclic cis-enaminoketones opens broad prospects for new chemical transformations in this series, for the synthesis from them of derivatives and analogs of neurotoxins of the pumiliotoxin C and gephyrotoxin families [7, 8], and also for other biologically active compounds with the required chirality and optical purity.

EXPERIMENTAL

The IR spectra were drawn on a UR 20 spectrometer. The ^1H NMR spectra were recorded on Tesla 60 and Bruker WM 400 spectrometers at room temperature in $CDCl_3$ solution, the internal standard being TMS. Chemical shifts are given in the δ scale. The UV spectra were recorded on a Varian Cary 15 spectrophotometer. Mass spectra were obtained on a MX 1321 spectrometer with direct insertion of the sample into the ion source at an evaporator temperature of 150-200°C and ionization energy 70 eV. The CD curves were drawn on a JASCO 20 spectropolarimeter in cuvettes of length 0.1 cm at 20°C. Specific rotation was measured on an EPO 1 polarimeter in cuvettes of length 0.25 dm at 20°C.

The data for the elemental analysis for C, H, and N corresponded to calculated values.

(+)-(1'S)-1-(α-Phenylethyl)-$\Delta^{9,10}$-octahydroquinolin-4-one (I) was obtained by the procedure of [9].

(+)-(1'S)-1-(α-Benzylethyl)-$\Delta^{9,10}$-octahydroquinolin-4-one (II) was similarly obtained by the procedure of [9]. $C_{18}H_{23}NO$. mp 124-125°C (from heptane). IR spectrum (in Nujol): 1615 (C=O), 1550 cm^{-1} (C=C). Mass spectrum: found M^+ 269, calculated M 269.

(+)-(1'S)-1-(sec-Butyl)-$\Delta^{9,10}$-octahydroquinolin-4-one (III, $C_{13}H_{21}NO$) was obtained similarly by the procedure of [9]. IR spectrum (thin film): 1638 (C=O), 1560 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 0.83 [3H, t, $N-CH(CH_3)CH_2C\underline{H}_3$], 1.07 [3H, d, $N-CH(C\underline{H}_3)CH_2CH_3$], 3.15 (2H, m, $N-CH(CH_3)C\underline{H}_2CH_3$], 3.77 ppm [1H, q, d, $N-C\underline{H}(CH_3)CH_2CH_3$]. Mass spectrum: found M^+ 207, calculated M 207. Picrate, mp 135-136°C (from ethanol). $C_{19}H_{24}N_4O_8$.

Diastereomers of 1-(S-α-phenylethyl)-3-methyl-$\Delta^{9,10}$-octahydroquinolin-4-one (IVa,b) were obtained by the procedure of [2].

Diastereomers of 1-(α-Phenylethyl)-3-ethyl-$\Delta^{9,10}$-octahydroquinolin-4-one (Va,b $C_{19}H_{25}NO$). A solution of (+)-(1'S)-1-(α-phenylethyl)-$\Delta^{9,10}$-octahydroquinolin-4-one (I) (1.04 g: 4 mmole) in absolute THF (20 ml) was added dropwise in a current of argon at −15°C to a solution of lithium diisopropylamide (8 mmole) obtained from a 1.3 M solution of lithium methyl (6.20 ml) in ether and diisopropylamine (0.81 g: 8 mmole) in absolute THF (10 ml). The reaction mixture was stirred at −15°C for 40 min and then ethyl iodide (1.25 g: 8 mmole) was added at the same temperature. The solution was stirred at −15°C for 1 h, diluted with water, and extracted with chloroform. The extract was dried over Na_2SO_4. The chloroform was evaporated and the residue (1.05 g) applied to a column packed with silica gel. The column was eluted with benzene−acetone, 8:1. Chromatographically uniform fractions were combined. (+)-1-(α-Phenylethyl)-3-methyl-$\Delta^{9,10}$-octahydroquinolin-4-one (Va)(0.28 g: 23%) and the (+) isomer (Vb) (0.50 g: 44%) were obtained.

Diastereomers of 1-(α-Phenylethyl)-3-isopropyl-$\Delta^{9,10}$-octahydroquinolin-4-one (VIa,b, $C_{20}H_{27}NO$). (+)-1-(α-Phenylethyl)-3-(isopropyl)-$\Delta^{9,10}$-octahydroquinolin-4-one (VIa) (0.29 g: 24%) and the (+) isomer (VIb) (0.41 g: 31%) were obtained analogously from lithium diethylamide (8 mmole), (+)-(1'S)-1-(α-phenylethyl)-$\Delta^{9,10}$-octahydroquinolin-4-one (I) (1.04 g: 4 mmole), and isopropyl iodide (0.90 g: 12 mmole).

Diastereomers of 1-(α-Phenylethyl)-3-benzyl-$\Delta^{9,10}$-octahydroquinolin-4-one (VIIa,b, $C_{24}H_{27}NO$). (+)-1-(α-Phenylethyl)-3-benzyl-$\Delta^{9,10}$-octahydroquinolin-4-one (VIIa) (0.49 g: 35%) and the (+) isomer (VIIb) (0.60 g: 39%) were obtained similarly from lithium diethylamide (8 mmole), (+)-(1'S)-1-(α-phenylethyl)-$\Delta^{9,10}$-octahydroquinolin-4-one (I) (1.04 g: 4 mmole), and benzyl bromide (1.37 g: 8 mmole).

Diastereomersof1-(α-Benzylethyl)-3-methyl-$\Delta^{9,10}$-octahydroquinolin-4-one(VIIIa,b,$C_{19}H_{25}NO$). 1-(α-benylethyl)-3-methyl-$\Delta^{9,10}$-octahydroquinolin-4-one (VIIIa) (0.52 g: 35%) and its isomer (VIIIb) (0.90 g: 65%) were obtained similarly from lithium diethylamide (16 mmole), (+)-(1'S)-1-(α-benzylethyl)-$\Delta^{9,10}$-octahydroquinolin-4-one (II) (2.10 g: 8 mmole), and methyl iodide (2.27 g: 16 mmole).

(1'S, 3S*)-(VIIIa): R_f 0.30 (Silufol, benzene−ethyl acetate, 4:1). mp 70-71°C (from hexane). IR spectrum (in Nujol): 1620 (C=O), 1560 cm^{-1} (C=C). UV spectrum (ethanol), λ_{max} (ε): nm (11000). Mass spectrum: round M^+ 283, calculated M 283.

(1'S, 3R*)-(VIIIb): R_f 0.26 (Silufol, benzene–ethyl acetate, 4:1). mp 81-82°C (from hexane). IR spectrum (in Nujol): 1630 (C=O), 1580 cm^{-1} (C=C). UV spectrum (ethanol), λ_{max} (ε): 330 nm (10000). Mass spectrum: found M^+ 283, calculated M 283.

Diastereomers of 1-sec-Butyl-3-methyl-$\Delta^{9,10}$-octahydroquinolin-4-one (IXa,b, $C_{13}H_{23}NO$). 1-sec-Butyl-3-methyl-$\Delta^{9,10}$-octahydroquinolin-4-one (IXa) (0.41 g: 50%) and its isomer (IXb) (0.40 g: 45%) were obtained similarly from lithium diethylamide (16 mmole), (1'S)-1-sec-butyl-$\Delta^{9,10}$-octahydroquinolin-4-one (III) (1.50 g: 8 mmole), and methyl iodide (2.27 g: 16 mmole).

(1'S, 3S*)-(IXa): R_f 0.30 (Silufol, benzene–ethyl acetate, 5:1). IR spectrum (thin film): 1640 (C=O), 1580 cm^{-1} (C=C). UV spectrum (ethanol), λ_{max} (ε): 325 nm (8500). Mass spectrum: found M^+ 209, calculated M 209.

(1'S, 3R*)-(IXb): R_f 0.26 (Silufol, benzene–ethyl acetate, 5:1). IR spectrum (thin film): 1620 (C=O), 1580 cm^{-1} (C=C). UV spectrum (ethanol), λ_{max} (ε): 326 nm (7800). Mass spectrum: found M^+ 209, calculated 209.

(+)-(3S*)-3-Methyl-$\Delta^{9,10}$-octahydroquinolin-4-one (X). (+)-(3S*)-3-Methyl-$\Delta^{9,10}$-octahydroquinolin-4-one (X) (0.13 g: 80%) was isolated on hydrogenolysis of (+)-(1'S, 3S*)-1-(α-phenylethyl-3-methyl-$\Delta^{9,10}$-octahydroquinolin-4-one (IVa) (0.26 g: 1 mmole) in methanol in the presence of palladium black. It had mp 122-123°C (from hexane). PMR spectrum ($CDCl_3$): 1.10 (3H, d, 3-CH_3), 5.33 ppm (1H, s, NH). CD spectrum (in heptane): $[\theta]_{330}$ +5500°. Mass spectrum: found M^+ 165, calculated M 165.

Similarly the (+)-enaminoketone (X) (0.11 g: 70%) was isolated on hydrogenolysis of (+)-(1'S, 3R*)-1-(α-phenylethyl)-3-methyl-$\Delta^{9,10}$-octahydroquinolin-4-one (IVb) (0.26 g: 1 mmole). It had mp 122-123°C (from hexane). CD spectrum (in heptane): $[\theta]_{330}$ +2500°. Mass spectrum: found M^+ 165, calculated M 165.

Diastereomers of 1-(α-Phenylethyl)-3-methyl-3'-butyl-$\Delta^{9,10}$-octahydroquinolin-4-one (XIa,b), $C_{22}H_{31}NO$). 1-(α-Phenylethyl)-3-methyl-3'-butyl-$\Delta^{9,10}$-octahydroquinolin-4-one (XIa) (0.20 g: 30%) and its isomer (XIb) (0.38 g: 70%) were obtained under standard conditions from lithium diisopropylamide (6 mmole), (+)-(1'S, 3R*)-1-(α-phenylethyl)-3-methyl-$\Delta^{9,10}$-octahydroquinolin-4-one (IVb)(0.80 g: 3 mmole), and butyl iodide (1.10 g: 6 mmole).

(1'S, 3S*)-(XIa): R_f 0.30 (Silufol, benzene–acetone, 4:1). mp 121-122°C (from heptane). IR spectrum (in Nujol): 1620 (C=O), 1580 cm^{-1} (C=C). UV spectrum (methanol), λ_{max} (ε): 323 (22,000), 205 nm (15,000). Mass spectrum: found M^+ 325, calculated M 325.

(1'S, 3R*)-(XIb): R_f 0.20 (Silufol, benzene–acetone, 4:1). mp 115-116°C (from hexane). UV spectrum (methanol), λ_{max} (ε): 322 (12,000), 205 nm (40,000). Mass spectrum: found M^+ 325, calculated M 325. IR spectrum (in Nujol): 1625 (C=O).

(−)-3-Methyl-3'-butyl-$\Delta^{9,10}$-octahydroquinolin-4-one (XIIa, $C_{14}H_{24}NO$). (−)-3-Methyl-3'-butyl-$\Delta^{9,10}$-octahydroquinolin-4-one (XIIa) (0.084 g: 70%) was isolated on hydrogenolysis of enaminoketone (XIa) (0.16 g: 0.5 mmole) in methanol in the presence of palladium black. R_f 0.20 (Silufol, benzene–acetone, 1:1). PMR spectrum ($CDCl_3$): 0.89 [3H, t, 3-$(CH_2)_3C\underline{H}_3$], 0.97 (3H, s, 3-$C\underline{H}_3$), 4.50 ppm (1H, s, NH).

(+)-3-Methyl-3'-butyl-$\Delta^{9,10}$-octahydroquinolin-4-one (XIIb, $C_{14}H_{24}NO$). The (+) enantiomer (XIIb) (0.08 g: 69%) was obtained analogously from enaminoketone (XIb) (0.16 g: 0.5 mmole). It had R_f 0.20 (Silufol, benzene–acetone, 1:1). PMR spectrum ($CDCl_3$): 0.89 [3H, t, 3-$(CH_2)_3C\underline{H}_3$), 0.97 (3H, s, 3-$C\underline{H}_3$), 4.50 ppm (1H, s, NH).

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