7. P. B. Kurapov and N. A. Klyuev, Khim. Geterotsikl. Soedin., No. 9, 1237 (1979).
8. P. B. Kurapov, N. A. Klyuev, O. N. Chupakhin, and I. I. Grandberg, Zh. Org. Khim., 16, 141 (1981).
9. P. B. Kurapov, N. A. Klyuev, I. I. Grandberg, O. N. Chupakhin, and V. I. Shilov, Zh. Org. Khim., 16, 175 (1981).
10. N. S. Kozlov, L. F. Gladchenko, V. A. Serzhanina, G. V. Vorob'eva, O. D. Zhikhareva, G. S. Shmanai, and R. D. Sauts, Khim. Geterotsikl. Soedin., No. 9, 1237 (1977).
11. A. F. Pozharskii, Khim. Geterotsikl. Soedin., No. 9, 1155 (1979).
12. I. I. Grandberg, Zh. Obshch. Khim., 33, 504 (1963).
13. N. A. Klyuev, E. S. Karavaeva, V. G. Zhil'nikov, and N. P. Bednyagina, Zh. Org. Khim., 17, 1757 (1981).
14. C. Parker, Photoluminescence of Solutions, Elsevier (1968).

REGIOSELECTIVE METHYLATION OF 1-BENZYL-$\Delta^{9,10}$-OCTAHYDRO-4-QUINOLONE*

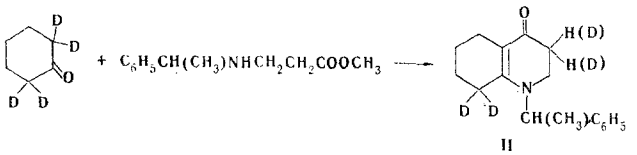
G. V. Grishina, I. F. Leshcheva, N. M. Sergeev, V. M. Potapov, and A. I. Vovk

UDC 547.831.8:542.953:543.42

The methylation of 1-benzyl-$\Delta^{9,10}$-octahydro-4-quinolone with methyl iodide in the presence of lithium diethylamide in tetrahydrofuran is a regioselective electrophilic substitution reaction, and, depending on the reaction conditions, takes place in the 3 or 8 position of the quinolone system. Deuteration under the same conditions takes place only in the 3 position.

Regioselective electrophilic substitution has been observed for N-substituted $\Delta^{9,10}$-octahydro-4-quinolone [1]. To ascertain the possibility of carrying out functional and asymmetric electrophilic substitution we investigated the effect of various factors on the direction of methylation of 1-benzyl-$\Delta^{9,10}$-octahydro-4-quinolone in the presence of strong bases.

We observed electrophilic substitution in a study of the ^{13}C NMR spectrum of the deutero derivative of 1-(1-phenylethyl)-$\Delta^{9,10}$-octahydro-4-quinolone (II). The synthesis of deuterated derivative II was carried out in order to assign the signals in the ^{13}C NMR spectrum of II (Table 1), since only the signals related to the C_2, C_3, C_4, C_9, and C_{10} atoms could be previously assigned by means of the literature data [2] and data from the spectra with incomplete decoupling of the protons. Deutero derivative II was obtained by condensation of 2,2,6,6-d_4-cyclohexanone with methyl 2-[N-(1-phenylethyl)amino]propionate:



II

In conformity with the scheme, it was assumed that the reaction proceeds with the formation of enamino ketone II, which contains deuterium atoms only in the 8 position. However, in the spectrum of deutero derivative II we observed a sharp decrease in the intensities of the two signals at 26.9 and 35.3 ppm.

For a more detailed analysis of the composition of the isotopomers we measured the triple ^{13}C-{^1H, ^2H} NMR spectra (see [3] for the method used to carry out these experiments).† It is apparent from the spectrum presented in Fig. 1 that three signals of unequal intensity were observed at 26.9 and 35.3 ppm. In conformity with the ^{13}C α-isotopic shifts (−0.35 ppm) due to replacement of hydrogen by deuterium [4], these signals can

*Communication 1 from the series "Methylated cis-enamino ketones."

†The triple {$^{13}C-^1H$, ^2H} NMR spectra were measured with the participation of Yu. K. Grishin and V. A. Chertkov.

M. V. Lomonosov Moscow State University, Moscow 117234. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 780-784, June, 1982. Original article submitted November 2, 1981.

0009-3122/82/1806-0589$07.50

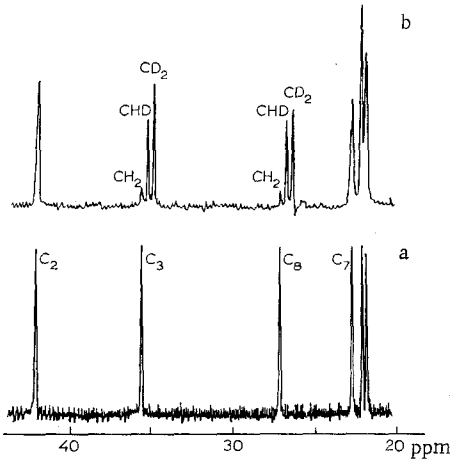


Fig. 1. ^{13}C NMR spectra of enamino ketone II at 20-40 ppm: a) undeuterated II, $^{13}C-\{^1H\}$ conditions; b) deuterated derivative II, $^{13}C-\{^1H, ^2H\}$ conditions.

be assigned to isotopomers that contain CH_2, CHD, or CD_2 fragments. Since the signal at 35.3 ppm was previously assigned to the C_3 atom, the remaining signal at 26.9 ppm was assigned to the C_8 atom. It should be noted that the signals at 22.3 and 41.9 ppm display a small (~−0.1 ppm) splitting due to β-isotopic effects [4]. This makes it possible to assign the indicated signals to the C_7 and C_2 atoms, respectively. The remaining signals at 21.5 and 21.9 ppm should be assigned to the C_5 and C_6 atoms; however, their mutually unambiguous assignment has not yet been established.

Thus a study of the spectra of deutero derivative II made it possible to almost completely assign the signals in the ^{13}C NMR spectrum of II. It was simultaneously ascertained that the condensation scheme presented above proceeds with the formation of compounds that contain deuterium not only in the 8 position but also in the 3 position.

Deuterium exchange in enamino ketone II also takes place at 20°C when it is allowed to stand for a week in D_2O–dioxane or in C_2H_5OD in the presence of catalytic amounts of $POCl_3$ or C_2H_5ONa, and a mixture of mono-, di-, tri-, and tetradeutero derivatives of enamino ketone II was formed; the degree of deuteration reaches 50-60%. We must also note that removal of the proton of the N-benzyl type was not observed.

The formation of a mixture of polydeuterated enamino ketones II in protic media constitutes evidence for a rather complex generation scheme and different reactivities of the aza anionic structures. To ascertain the direction of deprotonation and the possibility of carrying out planned electrophilic substitution in this series of compounds we made a detailed study of the methylation of 1-benzyl-$\Delta^{9,10}$-octahydro-4-quinolone (I) in aprotic media in the presence of strong bases.

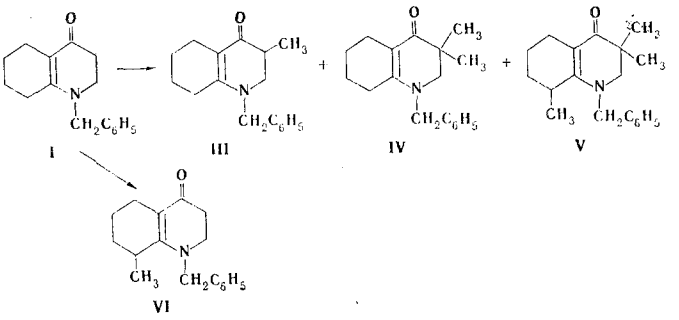
The methylation of enamino ketone I with methyl iodide takes place only when two to three equivalents of lithium diethylamide are used; the degree of metallation, which was determined by treatment of the lithium derivative of enamino ketone I with excess D_2O, reaches only 63%. From an analysis of the ^{13}C NMR and mass-spectrometric data we established the presence of deuterium in the 3 position of enamino ketone I. Methylation with methyl iodide of the lithium derivative of enamino ketone I obtained by the action of two equivalents of lithium diethylamide in tetrahydrofuran (THF) gave 1-benzyl-2-methyl-$\Delta^{9,10}$-octahydro-4-quinolone (III) (53%), the structure and the position of the methyl group in which were established by comparison of the spectral and chromatographic characteristics with those of enamino ketone III obtained by alternative synthesis.

The use of a threefold to fourfold excess of lithium diethylamide leads to an increase in the yield of enamino ketone III to 85%. The nature of the aprotic solvent (THF, ether, and benzene; a decrease in the yield of III to 30% is observed in hexane), the size of the grouping in the lithium amide (lithium diethyl-, diisopropyl-, and dicyclohexylamides), the temperature (−70, 0, and +20°C), and the metallation time (30 min to 6 h) have virtually no effect on the direction of methylation. Because of the low solubility of the lithium derivative of enamino ketone I obtained from lithium dicyclohexylamide, in dimethoxyethane the formation of 1-benzyl-3,3-dimethyl-$\Delta^{9,10}$-octahydro-4-quinolone (IV) becomes the chief reaction pathway; in addition to this, enamino ketone III and 1-benzyl-3,3,8-trimethyl-$\Delta^{9,10}$-octahydro-4-quinolone (V) are also formed.

TABLE 1. ^{13}C Chemical Shifts (δ, ppm) of Substituted $\Delta^{9,10}$-Octahydro-4-quinolones*

Compound	Position of the methyl groups	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	CH_3
I	—	48,4	35,4	189,9	21,8	21,5	22,1	27,0	159,5	106,8	
II	—	41,9	35,3	189,6	21,9	21,5	22,3	26,9	158,5	107,0	
III	3	54,7	37,8	192,4	21,7	21,4	21,9	26,6	158,1	105,5	12,6
IV	3, 3	60,7	39,0	196,2	22,2	22,0	22,5	27,2	157,9	105,0	22,5
V	3, 3, 8	59,8	38,7	196,6	22,0	19,9	29,2	30,0	162,1	103,6	22,7 17,0
VI	8	48,2	35,5	191,1	21,9	19,8	29,4	29,9	164,0	106,1	16,9

*Solutions in $CDCl_3$.



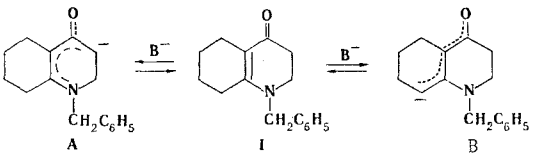
Another methylation pathway, which leads to substitution in the 8 position, is realized in the case of the reverse addition of 0.9 of an equivalent of lithium diethylamide to one equivalent of I and subsequent methylation; 1-benzyl-8-methyl-$\Delta^{9,10}$-octahydro-4-quinolone (VI) was isolated in 30% yield. An increase in the amount of the base to three equivalents again leads to methylation only in the 3 position. The formation of only 8-methyleneamino ketone VI is also observed in the case of successive treatment of enamino ketone I with 2.5-4 equivalents of the lithium diethylamide–hexametapol complex in a ratio of 1:1 in THF and methyl iodide.

The structure of enamino ketones III-VI and the position and number of methyl groups were established by means of ^{13}NMR spectroscopy (Table 1). The assignment of the protons was made with the aid of the spectra with incomplete decoupling of the protons and by comparison of the chemical shifts in the spectra of the unsubstituted and substituted compounds.

The classification of III-VI as cis-enamino ketones was confirmed by the presence of the readily identifiable (spectrally) enamino ketone chromophore [5]; the addition reactions that are characteristic for enamino ketones were not observed.

Thus the data obtained constitute evidence for a significant increase in the regioselectivity of electrophilic substitution in aprotic media and the possibility of carrying out the methylation of enamino ketone I in the 3 and 8 positions with 100% regioselectivity.

In conformity with the data obtained, it may be assumed that monodeprotonation of enamino ketone I under the influence of strong bases in aprotic media under kinetically controllable conditions (substitution in the 3 position) proceeds with the formation of aza anion A, whereas it takes place with the formation of aza anion B under thermodynamically controllable conditions (substitution in the 8 position):



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 of the compounds in ethanol were recorded with Cary-15 and Specord spectrophotometers. The ^{13}C NMR spectra of solutions in $CDCl_3$ were recorded with CFT-20 and XL-100 spectrometers. The mass spectra were obtained with an MKh-1303 mass spectrometer.

1-Benzyl- (I) and 1-α-phenylethyl-$\Delta^{9,10}$-octahydro-4-quinolone (II) were obtained by the method in [5].

2,2,6,6-Tetradeuterocyclohexanone. This compound was obtained in 92% yield by deuteration of 0.2 mole of cyclohexanone with 50 ml of D_2O containing 36 mmole of $POCl_3$ for 3 days at 20°C. The reaction mixture was neutralized with dry $KHCO_3$ and extracted twice with CH_2Cl_2, and the extract was dried with $MgSO_4$. Deuteration was repeated, and the mixture was worked up similarly and distilled in vacuo at 88-90°C (15 mm) to give a mixture of 5% 2,2,6-trideutero- and 92% 2,2,6,6-tetradeuterocyclohexanone according to mass spectrometry and PMR spectroscopy.

Preparation of a Mixture of Isotopomers of Mono-, Di-, Tri-, and Tetradeutero Derivatives of 1-(1-Phenylethyl)-$\Delta^{9,10}$-octahydro-4-quinolone. A) A mixture of 68 mmole of tetradeuterocyclohexanone, 34 mmole of methyl 2-[N-(1-phenylethyl)amino]propionate, 10 ml of absolute xylene, and a catalytic amount of CF_3COOH was refluxed for 20 h in a Dean–Stark apparatus, after which the solvent and excess cyclohexanone were removed in vacuo, and hexane was added to the residue. The resulting precipitate was removed by filtration to give 2.1 g (24%) of a mixture of 19% mono-, 42% di-, 32% tri-, and 7% tetradeutero derivatives of II (according to mass spectrometry) with mp 115-116°C (from hexane) and R_f 0.6 [benzene–acetone (1:1), Silufol].

B) A mixture of 10 mmole of enamino ketone II, 17 ml of D_2O, and 5 mmole of $POCl_3$ in 50 ml of absolute dioxane was maintained at 20°C for 6 days, after which it was neutralized with solid Na_2CO_3 and evaporated in vacuo to a volume of 2-3 ml. The concentrate was extracted with $CHCl_3$, and the extract was dried with $MgSO_4$. The solvent was removed, and the residue was recrystallized from heptane to give 0.9 g (36%) of a mixture of 30% mono-, 42% di-, 31% tri-, and 2% tetradeutero derivatives of enamino ketone II with mp 115-116°C.

C) A mixture of 2 mmole of enamino ketone II and 20 mmole of C_2H_5NaO in 9 ml of C_2H_5DO was maintained at room temperature for 6 days, after which the solvent was removed, 3 ml of D_2O was added to the residue, and the mixture was extracted with $CHCl_3$. The extract was dried with $MgSO_4$, the solvent was removed, and the residue was recrystallized from heptane to give 0.3 g (60%) of a mixture of 28% di-, 40% tri-, and 32% tetradeutero derivatives of enamino ketone II.

Typical Method for the Methylation of Enamino Ketone I. A solution of one equivalent of enamino ketone I in THF was added at −5°C in an argon atmosphere to a solution of three equivalents of lithium diethylamide in absolute THF. After 30 min, the mixture was treated with two equivalents of CH_3I, and the resulting mixture was stirred at 20°C for 2 h. The solvent was removed, ether was added, and the mixture was decomposed with water at 0°C. The mixture was extracted with chloroform (three 10-ml portions), and the extract was dried with $MgSO_4$. The solvent was removed, and the enamino ketone was isolated by means of column chromatography on Al_2O_3 or SiO_2.

1-Benzyl-3-methyl-$\Delta^{9,10}$-octahydro-4-quinolone (III). A) Methylation of 0.19 g (0.8 mmole) of enamino ketone I gave 0.11 g (85%) of enamino ketone III with mp 97-98°C (from heptane) and R_f 0.5 [benzene–acetone (4:1), Silufol]. IR spectrum (mineral oil): 1630 and 1568 cm^{-1}. UV spectrum (in ethanol): λ_{max} 333 nm (ε 14,800). Found: C 80.0; H 8.3%; M (mass spectrum) 255. $C_{17}H_{21}NO$. Calculated: C 80.0; H 8.3%.

B) A mixture of 10.7 g (0.1 mole) of benzylamine and 7.5 g (0.075 mole) of methyl methacrylate in 100 ml of CH_3OH was refluxed for 7 h, after which the solvent was removed, and the residue was distilled in vacuo to give 7.5 g (50%) of methyl 3-benzylamino-2-methylpripionate [6] with bp 150-152°C (10 mm) and n_D^{20} 1.5021. IR spectrum (film): 3340, 1748, and 1732 cm^{-1}.

C) A mixture of 3.2 g (16 mmole) of the amino ester obtained, 29.4 g (0.3 mole) of cyclohexanone, five drops of CF_3COOH, and 30 ml of absolute xylene was refluxed in a Dean–Stark apparatus for 5 h, after which the solvent and excess cyclohexanone were removed in vacuo, and the residue was cooled to 0° and treated with 15 ml of heptane. The precipitated crystals were removed by filtration to give 3.3 g (80%) of enamino ketone III, which with respect to its spectral and chromatographic properties was identical to the sample of enamino ketone III obtained by methylation of enamino ketone I; no melting-point depression was observed for a mixture of the two samples.

1-Benzyl-3,3-dimethyl-$\Delta^{9,10}$-octahydro-4-quinolone (IV). Methylation of 0.67 g (2.8 mmole) of enamino ketone I with CH_3I in the presence of 8.4 mmole of lithium dicyclohexylamide in 18 ml of dimethoxyethane gave a mixture of enamino ketones III and IV and 1-benzyl-3,3,8-trimethyl-$\Delta^{9,10}$-octahydro-4-quinolone (V), which was separated by means of column chromatography on SiO_2 by successive elution with benzene and benzene–ethyl acetate mixtures (10:1, 9:1, 8:1, and 6:1) to give 0.16 g (22%) of enamino ketone III with mp 87-98°C (from heptane) and 0.34 g (45%) of enamino ketone IV with mp 120-121°C (from heptane) and R_f 0.6 [benzene–ethyl acetate (4:1), Silufol]. IR spectrum (mineral oil): 1623 and 1565 cm^{-1}. UV spectrum (in ethanol):

λ_{max} 338 nm (ε 16,200). Found: C 80.6; H 8.8; N 5.4%; M (mass spectrum) 269. $C_{18}H_{23}NO$. Calculated: C 80.3; H 8.6; N 5.2%. Also isolated was 0.12 g (15%) of enamino ketone V with mp 153-154°C (from heptane). IR spectrum (mineral oil): 1632 and 1570 cm^{-1}. UV spectrum (in ethanol): λ_{max} 338 nm (ε 13,900). Found: C 80.1; H 8.7%; M (mass spectrum) 283. $C_{19}H_{25}NO$. Calculated: C 80.5; H 8.9%.

1-Benzyl-8-methyl-$\Delta^{9,10}$-octahydro-4-quinolone (VI). A) A solution of 9.22 g (0.9 mmole) of enamino ketone I in 5 ml of THF was treated successively at −5°C with 0.885 mmole of lithium diethylamide in THF and 0.9 mmole of CH_3I in 2 ml of THF. The usual workup and column chromatography on SiO_2 with elution with benzene–ethyl acetate (6:1) gave 0.077 g (34%) of enamino ketone VI with mp 64-65°C (from pentane) and R_f 0.4 [benzene–acetone (4:1), Silufol]. IR spectrum (in mineral oil): 1629 and 1562 cm^{-1}. UV spectrum (in ethanol): λ_{max} 342 nm (ε 8500). Found: C 80.3; H 8.4%; M (mass spectrum) 255. $C_{17}H_{21}NO$. Calculated: C 80.0; H 8.3%. Also isolated was 0.11 g (50%) of starting enamino ketone I.

B) Methylation of 0.12 g (0.5 mmole) of enamino ketone I in the presence of 2.5 mmole of the lithium diethylamide–hexametapol complex in a ratio of 1:1 in 10 ml of THF gave 0.05 g (40%) of enamino ketone VI with mp 64-65°C (from pentane) and 0.05 g (43%) of enamino ketone I.

1-Benzyl-3-deutero-$\Delta^{9,10}$-octahydro-4-quinolone. A solution of 0.5 g (2.1 mmole) of enamino ketone I in 3 ml of THF was added to a solution of 6 mmole of lithium diethylamide in 30 ml of THF, and the reaction mixture was treated with 5 ml of D_2O after 30 min. The resulting crude enamino ketone was purified with a short column filled with Al_2O_3 by elution with benzene–ethyl acetate (1:1) to give 0.41 g (82%) of enamino ketone I, which, according to mass spectrometry, was a mixture of 34% of enamino ketone I and 57% of its 3-mono derivative and 9% of its dideutero derivative.

LITERATURE CITED

1. G. V. Grishina, A. I. Vovk, and V. M. Potapov, Khim. Geterotsikl. Soedin., No. 11, 1565 (1979).
2. G. C. Levy and G. L. Nelson, Carbon-13 Nuclear Magnetic Resonance for Organic Chemists, Wiley, New York (1972).
3. V. A. Roznyatovskii, V. A. Chertkov, and Yu. K. Grishin, Zavod. Lab., 46, 805 (1980).
4. N. M. Sergeev, NMR Spectroscopy for Organic Chemists [in Russian], Izd. MGU, Moscow (1981), Chapter 4.
5. V. M. Potapov, G. V. Kiryushkina, G. N. Koval', and G. P. Tokmakov, Khim. Geterotsikl. Soedin., No. 4, 541 (1972).
6. L. Horii, C. Iwata, and G. Tamura, Chem. Pharm. Bull., 10, 940 (1962).