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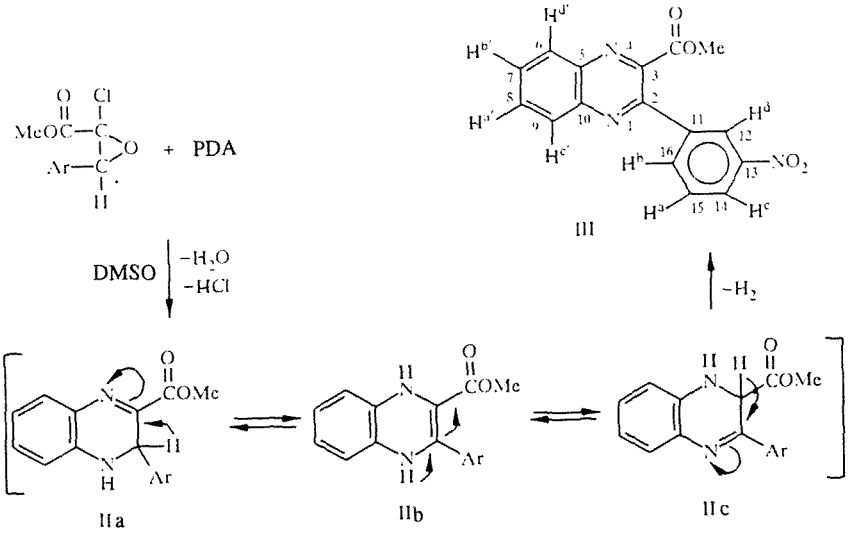
CONDENSATION OF METHYL 2-CHLORO-3-(3-NITROPHENYL)-2,3-EPOXYPROPIONATE WITH 1,2-PHENYLENE DIAMINE

V. A. Mamedov, L. V. Krokhina, and A. V. Il'yasov

It is established that the α-chloroepoxide methyl 2-chloro-3-(3-nitrophenyl)-2,3-epoxypropionate, in contrast to its α-chloroketone isomer methyl 3-(3-nitrophenyl-3-chloro-2-oxopropionate, forms 2-(3-nitrophenyl-3-methoxycarbonylquinoxaline in reaction with 1,2-phenylene diamine, whereas the condensation of the α-chloroketone with 1,2-phenylene diamine gives 3-(α-chloro-3-nitrobenzyl)-2-oxo-1,2-dihydroquinoxaline.

We showed earlier that in the derivatives of 3-aryl-3-chloro-2-oxopropionic acids the substitution of the ester group by the amino group in reaction with 1,2-phenylene diamine (PDA) leads to different substituted quinoxalines: esters of this acid give 3-(α-chlorobenzyl)-2-oxo-1,2-dihydroquinoxalines and amides give 3-aryl-2-(N,N-dialkylcarbamoyl)-1,4-dihydroquinoxalines [1, 2]. In so far as the α-chloroketones studied in these reactions were obtained as a result of the isomerization of the corresponding α-chloroepoxides under Darzan Condensation conditions [3], it became necessary to study the behavior of methyl 2-chloro-3-(3-nitrophenyl)-2,3-epoxypropionate (I) [3] as a precursor to methyl 3-(3-nitrophenyl)-3-chloro-2-oxopropionate (II) in reaction with PDA.

Stirring α-chloroepoxide I with PDA in DMSO at 20°C leads to the formation of a crystalline product, the spectral data (IR, ^{1}H NMR) of which correspond with 2-(3-nitrophenyl)-3-methoxycarbonylquinoxaline (III).



The IR spectrum of compound III shows absorption bands at 1540 cm^{-1} for the C=N group and two bands at 1555 and 1375 cm^{-1} corresponding to the asymmetric and symmetrical oscillations of the NO_2 group, as well as an intense absorption band at 1715 cm^{-1} region belonging to the C=O group. In the ^{1}H NMR spectrum the protons of the quinoxaline ring and also the 3-nitrophenyl group, each appear separately in the form of a strongly bonded quadruplet ABCD system in

Institute of Organic and Physical Chemistry, A. E. Arbuzov Kazan Scientific Center, Russian Academy of Sciences, Kazan, 420083. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1105-1108, August, 1994. Original article submitted July 18, 1994.

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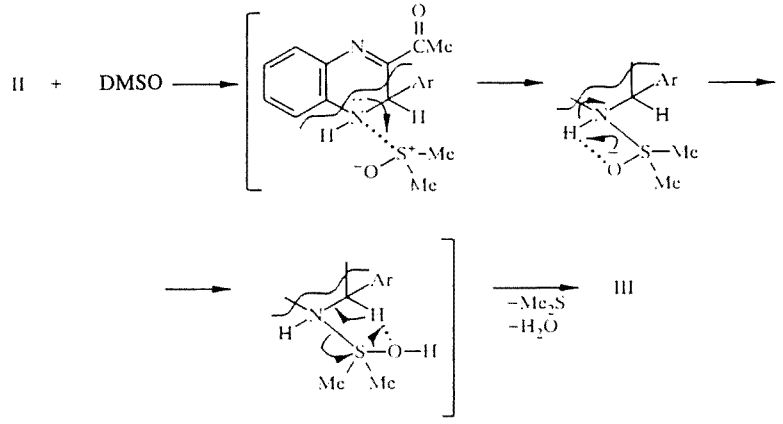
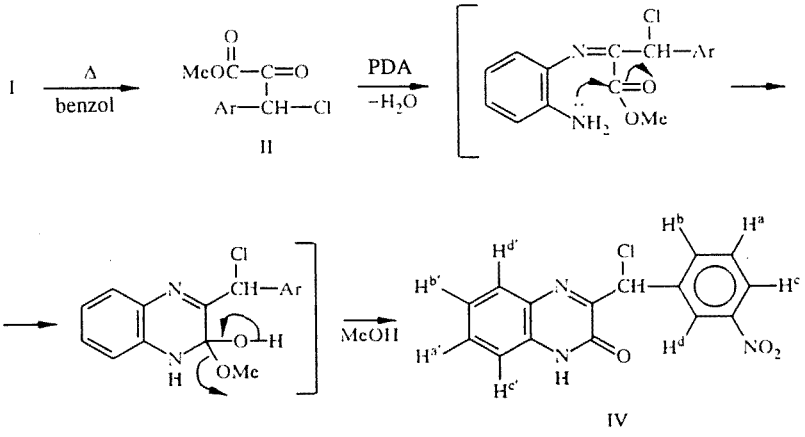
the 7.92-8.67 ppm region. The multiplicity of the signals resulting from the spin–spin interaction of ^{13}C and the ^{1}H both through the single bond $^{1}J_{CH}$ and the long-range $^{2}J_{CH}$ allows the unambiguous assignment of the carbon signals of quinoxaline III in the ^{13}C NMR spectrum. The substituents in positions 2 and 3 disrupt the symmetry of the quinoxaline ring, as a result of which practically all of the carbon atom signals are distinguishable. The signals of the quaternary carbons C_2, C_3, C_5, and C_{10}, which occur in the 142.56, 147.91, 153.20, and 151.64 ppm, respectively, are not detected in the $^{1}J_{CH}$ splitting, but occur in the long-range constants $^{3}J_{CH}$ = 1.1 Hz for the C_2 atom and $^{2}J_{CH}$ = 8.2 Hz for the C_5 and C_{10} atoms. Because of $^{1}J_{CH}$ and $^{2}J_{CH}$, the signals for C_6 and C_9 occur as doublets in the 132.80 ppm region, and the C_7 and C_8 occur as doublets of triplets in the 127.81 and 126.86 ppm regions. The chemical shifts and spin–spin coupling constants for the remaining carbon atoms are given in the Experimental Part.

The transformation of the intermediately-formed dihydroquinoxaline IIa, which evidently exists in the imino–enamine tautomers (IIa ⇄ IIb ⇄ IIc), into quinoxaline III in DMSO solution indicates that the solvent appears in the role of an oxidant, which probably can be described in the following scheme:



The presence of the ester group in product III from the reaction of α-epoxide I with PDA is somewhat surprising, since, under the reaction conditions, it is usually subject to intramolecular amidation, as shown in the example of the condensation of PDA with α-chloroketone II, obtained by thermal isomerization of the α-chloroepoxide I.

The presence of signals from the CH and NH groups in the 6.96 and 12.81 ppm regions, and also the absence of a signal for the C(O)OMe group in the ^{1}H NMR spectrum of compound IV confirms the formation of the 1,2-dihydroquinoxaline IV by intramolecular amidation of the ester group of the intermediately-form adduct, which is in turn obtained as a result of the attack of the NH_2 group of PDA on the carbonyl group of the α-chloroketone II.



The preservation of the ester group in quinoxaline III may occur because the initial nucleophilic attack of the NH_2 group of PDA takes place on the sterically less hindered tertiary carbon atom of the α-chloroepoxide I and the formation of the intermediate compound impedes the interaction of the ester group with the second amino group of PDA.

The results of these reactions and also of our earlier data [1, 2] based on the earlier literature [4, 5], allow us to conclude that in the reactions of halo-substituted esters of 2-oxopropionic acids and/or of 2,3-epoxypropionic acids with PDA, amidation of the ester group does not take place in the initial step

EXPERIMENTAL

The NMR spectra of compounds III and IV were recorded on a Bruker MSL-400 instrument with a working frequency of 400.13 MHz for ^1H and 100.6 MHz for ^{13}C. The ^1H NMR spectrum of compound II was determined with a Varian-60 spectrometer. The IR spectra were recorded with a UR-20 spectrometer in mineral oil. Melting points were determined with a Boethius micro hot-stage.

Elemental analysis data for C, H, N, and Cl corresponded with the calculated values.

Methyl 2-Chloro-3-(3-nitrophenyl)-2,3-epoxypropionate (I). To a mixture of 15.1 g (0.1 mole) of 3-nitrobenzaldehyde and 14.3 g (0.1 mole) of methyl dichloroacetate in 100 ml of ether at 0-5°C under an atmosphere of dry argon over 1.5 h was added a solution of 3.9 g (0.1 g-atom) of K in 100 ml of *t*-BuOH. The mixture was stirred for about 4 h, then was kept for 24 h at 20°C, and the *t*-BuOH was evaporated under vacuum. To the remaining mass was added 5% aqueous NaCl, and the mixture was extracted with chloroform (3 × 75 ml), and dried with $MgSO_4$. The solvent was evaporated, and the resulting mass deposited crystals upon standing. Filtration and washing with ether gave mp 108-109°C [3].

2-(3-Nitropheny)-3-methoxycarbonylquinoxaline (III). A mixture of equimolar amounts of α-chloroepoxide I and PDA in DMSO was stirred at 20°C for 24 h. The resulting precipitate was filtered off and washed with ether to give compound IV in 80% yield with mp 193-194°C. IR spectrum: $\nu_{C=O}$ 1715, $\nu_{C=N}$ 1540. ^1H NMR spectrum (DMSO-d_6): 3.96 (3H, s, CH_3O); 7.95 (1H, t, H_a, $^3J_{ab} = {}^3J_{ac} = 8.0$); 8.08-8.19 (2H, m, H_a and H_b); 8.26 (1H, dt, H_b, $^3J_{ab} = 8.0$, $^4J_{bc} = {}^4J_{bd} = 1.8$); 8.37 (2H, dd, H_c and H_d, $^3J_{b'd'} = {}^3J_{a'c'} = 8.35$, $^4J_{b'c'} = {}^4J_{a'd'} = 2.7$); 8.51 (1H, dt, H_c, $^3J_{ac} = 8.0$, $^4J_{cb} = {}^4J_{cd} = 1.8$); 8.66 (1H, t, H_d, $^4J_{dc} = {}^4J_{db} = 1.8$). ^{13}C NMR spectrum (DMSO-d_6): 56.65 (q, $^1J = 148.9$, CH_3); 126.86 (dt, $^1J = 169.2$, $^2J = 5.1$, C_7); 127.81 (dt, $^1J = 169.2$, $^2J = 5.1$, C_8); 132.80 (dd, $^1J = 167.1$, $^2J = 5.6$, C_6 and C_9); 133.82 (d, $^1J = 158.9$, C_{12}); 135.40 (dd, $^1J = 161.2$, $^2J = 8.5$, C_{16}); 136.31 (dd, $^1J = 167.3$, $^2J = 8.8$, C_{14}); 138.61 (dt, $^1J = 160.6$, $^2J = 5.6$, C_{15}); 142.56 (d, $^3J = 1.1$, C_2); 143.28 (dd, $^2J = 8.9$, C_{11}); 145.18 (dd, $^2J = 8.6$, C_{13}); 147.92 (s, C_3); 151.64 (d, $^2J = 8.4$, C_{10}); 153.20 (d, $^2J = 8.2$, C_5); 169.42 (s, C=O).

Isomerization of α-Chloroepoxide I into α-Chloroketone II. A solution of 0.5 mole of α-chloroepoxide I in 50 ml of benzene was boiled until the disappearance in the ^1H NMR spectrum of the signal in the 4.83 ppm region (3 h). The benzene was evaporated under vacuum and the residue was distilled to give compound II in 95% yield, bp 170-174°C/0.02 mm Hg. IR spectrum [$(CD_3)_2C$=O]: 3.80 (3H, s, CH_3O); 6.43 (1H, s, CHCl); 7.40-8.33 (4H, m, *t*-O_2N-C_6H_4).

3-(α-Chloro-3-nitrobenzyl)-2-oxo-1,2-dihydroquinoxaline (IV). A solution of equimolar amounts of α-chloroketone II and PDA in CH_3COOH was stirred at 20°C for 2 h. The resulting precipitate was filtered off, washed with ether, dried, and recrystallized from DMSO to give mp 239-240°C. IR spectrum (ν, cm^{-1}): 2500-3200 (NH), 1675 (C=O). ^1H NMR (DMSO-d_6): 6.96 (1H, s, CH); 7.41 (2H, m, $H_{a'}$ and $H_{c'}$); 7.67 (1H, mult. t, $H_{b'}$, $^3J_{b'a'} = {}^3J_{b'd'} = 7.5$, $^4J_{b'c'} = 1.4$); 7.79 (1H, t, H_a, $^3J_{ab} = {}^3J_{ac} = 8.0$); 7.86 (1H, mult. d, $H_{d'}$, $^3J_{d'b'} = 7.5$, $^4J_{d'a'} = 1.4$); 8.15 (1H, d, H_b, $^3J_{ab} = 8.0$); 8.31 (1H, dt, $^3J_{ca} = 8.0$, $^4J_{cd} = {}^4J_{cb} = 1.8$); 8.57 (1H, t, H_d, $^4J_{dc} = {}^4J_{db} = 1.8$); 12.81 (1H, br. s, NH).

Carrying out the reaction of α-chloroketone II and PDA in benzene or in DMSO also gave compound IV.

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