REACTION OF 8-SUBSTITUTED 3-PHENYL-5-METHYL-2-OXA-1-AZA-BICYCLO[3.3.0]OCTANES WITH NUCLEOPHILIC REAGENTS

I. E. Chlenov, Yu. B. Salamonov,
and V. A. Tartakovskii

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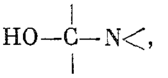
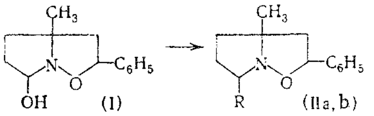
The purpose of the present paper was to study the reaction of 8-substituted 3-phenyl-5-methyl-2-oxa-1-azabicyclo[3.3.0]octanes with nucleophilic reagents.

The 8-hydroxy derivative (I) contains the fragment  $HO-\overset{|}{\underset{|}{C}}-N<$, in which, it could be assumed, the OH group will be replaced by the moieties of the corresponding nucleophilic reagents when (I) is reacted with alcohols, amines, and a number of carbanions.

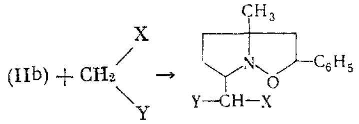
The hydroxyl group in (I) is easily replaced by the methoxy group to give (IIa) when (I) is refluxed with methanol, and by the propylamino group to give (IIb) when (I) is refluxed with propylamine in benzene.



$R = OCH_3$ (a); NHC_3H_7 (b)

We were unable to isolate (IIa, b) in an analytically pure form, and their structure was established on the basis of the NMR spectra.

We found that (I) and (IIa) do not react with active methylene compounds, like methyl nitroacetate (IIIa), ethyl cyanoacetate (IIIb), acetylacetone (IIIc), and acetoacetic ester (IIId), either without a catalyst or in the presence of BF_3 etherate. However, in the case of (IIb) we were able to obtain the condensation products (IVa-d) with all of the (IIIa-d) compounds. Judging by the NMR spectra, (IVa, b, d) are obtained as at least two steric isomers, while (IVc) is obtained as one isomer.



(IVa-d)

$X = COOCH_3$, $Y = NO_2$ (a); $X = COOC_2H_5$, $Y = CN$ (b);
$X = Y = COCH_3$ (c), $X = COOC_2H_5$, $Y = COCH_3$ (d)

The most active in this reaction are (IIIa, b) which react with (IIb) when the reactants are refluxed in either benzene or CH_3CN. In the case of (IIIc, d) it is necessary to use BF_3 etherate as a catalyst. This difference is apparently associated with the fact that the acidity of (IIIc) (pK_a 9.0) and (IIId) (pK_a 10.7) [1] is inadequate for protonation of the exocyclic nitrogen atom in (IIc), which makes it impossible to remove the amine moiety. When a catalyst is used the amine moiety is removed as the complex with BF_3,

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while the bicyclic immonium cation that is formed here apparently reacts with the enol form of (IIIc, d) to give the reaction products. Indirect confirmation of this assumption can be the fact that the best results were obtained when the reactions were run in hexane, a solvent in which the amount of the enol form of (IIIc, d) is maximum [2].

The fact that the reaction with (IIIa) can be run without a catalyst is explained by its high acidity (Pk$_a$ 5.8) [3]. From this standpoint, the reasons for the high reactivity of (IIIb) remain unclear, since its acidity (pK$_a$ 10.5) [1] approaches the acidity of (IIIc, d). The negative result when (I) and (IIa) are reacted with (IIIa-d) is apparently explained by the fact that the electrophilic particles (proton or BF_3) do not attack the exocyclic oxygen function, and instead combine with the nitrogen atom of the bicycle.

EXPERIMENTAL METHOD

Preparation of (I).* To a stirred solution of 0.5 g of 6-methyl-8-phenyl-2, 9-dioxa-1-azabicyclo[4.3.0]nonane [5] in 15 ml of abs. benzene was added in drops, below 6°C, a solution of 0.35 ml of BF_3 etherate in 2.5 ml of abs. benzene, after which the mixture was stirred at ~20° for 40 min, neutralized with a solution of 0.49 g of Na_2CO_3 in 40 ml of water, the aqueous layer was separated, extracted with ether, the ether—benzene extracts were dried over $MgSO_4$, and the solvents were removed. We obtained 0.43 g (86%) of (I), mp 92-96° (4:1 hexane—CCl_4). Found: C 71.23; H 7.77; N 6.70%. $C_{13}H_{17}NO_2$. Calculated: C 71.23; H 7.76; N 6.39%. Infrared spectrum (ν, cm^{-1}): 3200 (OH). NMR spectrum (in $CDCl_3$, δ, ppm): 1.42 s (CH_3); 5.04 m (PhCHO, OCHN<); 4.45 (OH) 1.11-2.58 m ($3CH_2$).

Preparation of (IIa). A solution of 0.32 g of (I) in 15 ml of abs. methanol was refluxed for 6 h and then the methanol was distilled off. We obtained 0.34 g (100%) of (IIa) as a yellow oil. The compound could not be obtained analytically pure. NMR spectrum (in $CHCl_3$, δ, ppm): 1.42 s (CH_3); 4.98 q (PhCHO); 4.55 m (OCHN<); 3.42 s (OCH_3); 1.72-2.58 m ($3CH_2$).

Preparation of (IIb). A mixture of 0.55 g of (I) and 0.52 g of propylamine in 15 ml of abs. benzene was refluxed for 6 h, after which the solvent was distilled off, the residue was extracted with hexane, and the hexane was removed. We obtained 0.63 g (97%) of (IIb) as a brown oil. The compound could not be obtained analytically pure. Infrared spectrum (ν, cm^{-1}): 3300 (NH). NMR spectrum (in $CHCl_3$, δ, ppm): 0.87 t (CH_3); 1.33 s (CH_3C); 1.13-3.06 m ($5CH_2$, NH); 4.06 m (NCHN); 5.00 q (PhCHO).

Preparation of (IVa). A mixture of 0.63 g of (IIb) and 0.29 g of (IIIa) in either 15 ml of abs. benzene or CH_3CN was refluxed for 2 h and then the solvent was distilled off. We obtained 0.8 g (100%) of (IVa), mp 110-112° (from MeOH). Found: C 60.34; H 6.43; N 8.66%. $C_{16}H_{20}N_2O_5$. Calculated: C 60.00; H 6.43; N 8.66%. Infrared spectrum (ν, cm^{-1}): 1360, 1575 (NO_2); 1775 (C = O). NMR spectrum (in $CHCl_3$, δ, ppm): 1.28 s and 1.29 s (CH_3C); 1.68-2.51 m ($3CH_2$); 3.76 s and 3.77 s ($COOCH_3$); 4.00 m (CHN<); 5.00-5.40 m (PhCHO, $CHNO_2$).

Preparation of (IVb). A mixture of 0.17 g of (IIb) and 0.07 g of (IIIb) in 15 ml of abs. benzene was refluxed for 5 h, the benzene was distilled off, the residue was extracted with hexane, and the hexane was removed. We obtained 0.16 g (78%) of (IVb), mp 95-96° (from ethanol). Found: C 67.86; H 7.03; N 9.23%. $C_{18}H_{22}N_2O_3$. Calculated: C 67.77; H 6.98; N 9.28%. Infrared spectrum (ν, cm^{-1}): 1750 (C = O), 2265 ($C \equiv N$). NMR spectrum (in $CHCl_3$, δ, ppm): 1.20 t (CH_3); 1.32 s and s (CH_3C), 3.66 m (CHN<); 1.52-2.49 m ($3CH_2$); 3.78-4.34 m (OCH_2, $CHC \equiv N$); 5.01 m (PhCHO).

Preparation of (IVc). To a solution of 0.42 g of (IIb) and 0.82 g of (IIIc) in 6 ml of hexane was added 3-5 drops of BF_3 etherate, the mixture was kept for 2 days, the hexane was distilled off, and the residue was chromatographed on an Al_2O_3 column (eluant = 10:1 benzene—ethanol). We obtained 0.31 g (64%) of (IVc), mp 102-103° (from 75% ethanol). Found: C 71.73; H 8.01; N 4.68%. $C_{18}H_{23}NO_3$. Calculated: C 71.76; H 7.64; N 4.65%. Infrared spectrum (ν, cm^{-1}): 1700 (C = O). NMR spectrum (in $CHCl_3$, δ, ppm): 1.26 s (CH_3C); 2.20 s ($CH_3C=O$); 1.62-2.54 m ($3CH_2$); 3.90 m (COCH, CHN<); 5.12 q (PhCHO).

Preparation of (IVd). A mixture of 0.42 g of (IIb), 1.05 g of (IIId), and 3-5 drops of BF_3 etherate in 6 ml of hexane was kept for 4 days, the hexane was removed, the excess (IIId) was vacuum-distilled using an oil pump, the residue was extracted with hexane, the solvent was removed, and the product was isolated by preparative TLC on LSL silica gel 5/40 (eluant = 10:1 benzene—EtOH). We obtained 0.18 g (34%) of (IVd), mp 65-66° (from 75% ethanol). Found: C 68.80; H 7.76; N 4.08%. $C_{19}H_{25}NO_4$. Calculated: C 68.88; H 7.55; N 4.23%. Infrared spectrum (v, cm^{-1}): 1720 ($C=_0$), 1745 (COO). NMR spectrum (in $CHCl_3$, δ, ppm):

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* See [4] for preliminary communication.

120 t (CH_3); 1.29 s (CH_3C); 1.71-2.6 m ($3CH_2$); 2.24 s and 2.27 s ($CH_3C=O$); 3.64-4.33 m ($CHN<$, $CHC=O$, OCH_2); 5.09 q (PhCHO).

CONCLUSIONS

1. When 5-methyl-3-phenyl-8-hydroxy-2-oxa-1-azabicyclo[3.3.0]octane is reacted with methanol and propylamine the hydroxyl group is respectively replaced by the methoxy and N-propylamine group.

2. 5-Methyl-3-phenyl-8-(N-propylamino)-2-oxa-1-azabicyclo[3.3.0]octane reacts with methyl nitroacetate and ethyl cyanoacetate without a catalyst, and with acetylacetone and acetoacetic ester in the presence of BF_3 etherate as the catalyst, to give condensation products.

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