UDC 547.244.+26+ 28+333.3+ 466+ 491+ 822+ 834

QUARTERNIZATION OF 3-(N-MORPHOLINO)-3-CYANOQUINUCLIDINE

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Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 29, No. 2, pp. 60 – 61, February, 1995.

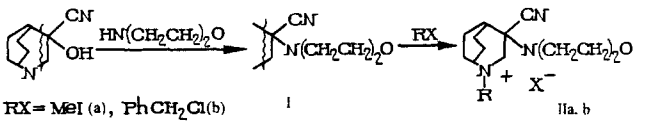
Original article submitted February 1, 1994.

3-(N-morpholino)-3-cyanoquinuclidine has been shown to form only 1-methyl-3-(N-morpholino)-3-cyanoquinuclidinium iodide or 1-benzyl-3-(N-morpholino)-3-cyanoquinuclidinium chloride when treated with iodomethane (1 : 1 or 1 : 2.3) or benzene chloride (1 : 1), respectively. The direction of quarternization is determined using ^{1}H NMR spectroscopy.

3-Dialkylamino-3-cyanoquinuclidines readily formed from 3-hydroxy-3-cyanoquinuclidine are valuable starting materials for further introduction of functional groups into the quinuclidine ring. Transformations of 3-dialkylamino-3-cyanoquinuclidines were reported involving the elimination of the CN-group [1]. However, the reactions with the elimination of the dialkylamino group should be of no less interest, because they lead to Δ^2-cyanoquinuclidine, which is not readily available. A highly developed procedure for the elimination of the dialkylamino group is the Hofmann reaction for which conversion of tertiary amine to quarternary salt is necessary.

Although the nucleophilicity of the quinuclidine nitrogen is known to exceed the nucleophilicity of tertiary amines [2 – 5], the presence of the second amino fragment in 3-dialkylamino-3-cyanoquinuclidines required the evaluation of their relative abilities for quarternization. 3-Morpholino-3-cyanoquinuclidine was used as a model, as it is convenient and has an easily interpreted spectrum; iodomethane was selected as the second component. In order to eliminate distortions in the true ratio of *mono-* and *bis*-quarternary salts caused by their different solubilities, the reaction mixture was brought to homogeneity by heating or adding methanol upon completion of the reaction; an aliquot was evaporated to dryness, dissolved in D_2O, and analyzed using PMR spectroscopy.

When the diamine – MeI ratio is 1 : 1 (in chloroform or ethanol) and 1 : 2.3 (in a chloroform – ethanol mixture), methylation is directed exclusively at the quinuclidine nitrogen. This follows from the invariant position of signals from the α-protons of the morpholine ring when going from I to IIa. At the same time, the signals from the quinuclidine protons are shifted downfield. The shift decreases as the protons are further removed from he nitrogen (α > β > γ). Similar results have been obtained in the reaction of I with benzyl chloride.



Thus, the observed regiospecificity of N-alkylation of I does not allow us to use quarternization for conversion of the dialkylamino group to the readily eliminated fragment required for transformation to Δ^2-cyanoquinuclidine. Application of the Cope reaction to the N-oxide IIb may be an alternative route.

EXPERIMENTAL PART

3-Morpholino-3-cyanoquinuclidine (I). A mixture of 3-hydroxy-3-cyanoquinuclidine (30 g, 0.197 mole), morpholine (60 ml, 0.6 mole), and benzene (120 ml) is boiled in a flask fitted with a Dean and Stark distillation head until water separation is complete, then the solution is evaporated until dry and the residue is crystallized twice from ethylacetate to produce product I (25.1 g, 61%, m. p.114 – 116°C) (literature m. p. 107 – 109°C [1]). PMR (200 MHz, D_2O, dioxane as internal standard, δ, ppm.): 1.40 – 1.20 (m, 1H), 1.75 – 1.53 (m, 3H, $H_{\beta'} + H_{\beta''}$), 2.18 (quint, H_γ, J = 0.8 Hz), 2.53 – 2.34 (m, 4H, NCH_2CH_2), 2.75 – 2.53 (m, 4H, $H_{\alpha'} + H_{\alpha''}$), 2.79 (d, $H_{\alpha1}$, J = 3.5 Hz), 2.99 (d, $H_{\alpha2}$, J = 3.5 Hz), 3.61 (t, 4H, $N(CH_2CH_2)O$, J = 1.2 Hz).

1-Methyl-3-morpholino-3-cyanoquinuclidinium iodide (IIa). A solution of I (0.666 g, 0.003 mole) in chloroform (1 ml) and iodomethane (0.426 g, 0.003 mole) is held for 24 h at room temperature. Product IIa (0.956 g, 87%) is obtained

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after filtering and drying. Recrystallization from 99% ethanol yields colorless crystals (m. p. 175 – 177°C (decomp.)) which are soluble in water, in alcohols (with heating), and moderately soluble in chloroform. When ethanol (4 ml) is used instead of chloroform (1 ml), the yield of IIa is 1.07 g (98%); and using a mixture of dry ether and chloroform (10 ml + 2 ml) results in 99% yield of IIa. PMR (δ, ppm): 1.88 – 1.68 (1H, m); 2.20 – 1.98 (3H, m, $H_{\beta'} + H_{\beta''}$); 2.58 – 2.32 [4H, m, $N(CH_2CH_2)O$]; 2.62 (H_γ, quint, J = 0.8 Hz); 2.88 ($N^+–CH_3$, s); 3.50 – 3.18 (4H, m, $H_{\alpha'} + H_{\alpha''}$); 3.57 ($H_{\alpha1}$, d, J = 3.5 Hz), 3.62 [4H, t, $N(CH_2CH_2)O$, J = 1.2 Hz); 3.74 ($H_{\alpha2}$, d, J = 3.5 Hz).

Iodomethane (1.7 g, 0.014 mole) was added to a solution of I (1.332 g, 0.006 mole) in a chloroform – ethanol mixture (6 ml + 1 ml) and held at room temperature for 2 days. Product IIa (1.9 g, 86%) was obtained as a precipitate. The mother liquor contained only IIa, the bis-iodide was not formed.

1-Benzyl-3-morpholino-3-cyanoquinuclidinium chloride (IIb). A solution of I (1.332 g, 0.006 mole) in 2-propanol (10 ml) and benzyl chloride (0.83 g) was kept at room temperature for 24 h. Product IIb (1.97 g, 95%) was obtained as a colorless precipitate [m. p. 227 – 229°C (decomp.)]. PMR (δ, ppm.): 1.86 – 1.64 (1H, m); 2.20 – 1.98 (3H, m, $H_{\beta'} + H_{\beta''}$); 2.58 – 2.32 [4H, m, $N(CH_2CH_2)$]; 2.64 (H_γ, quint, J = 0.8 Hz,); 3.46 – 3.30 (4H, m, $H_{\alpha'} + H_{\alpha''}$); 3.51 ($H_{\alpha1}$, d, J = 3.5 Hz); 3.64 [4H, t, $N(CH_2CH_2)O$, J = 1.2 Hz); 3.69 ($H_{\alpha2}$, d, J = 3.5 Hz); 4.31 [2H, s, $N^+–CH_2Ph$); 7.50 – 7.30 (5H, m, C_6H_5).

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