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The Synthesis of 2-Amino-3-cyano Derivatives of 4,5-Dihydrofuran and 5,6-Dihydro-4H-pyran, and their Transformation to Lactones

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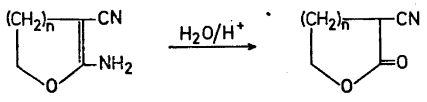
Recently, the synthesis of some substituted 2-amino-3-cyano-4,5-dihydrofurans from the sodium derivative of malonitrile and substituted ethylene oxides was reported.[1] This prompts the following report of a convenient preparation of 2-amino-3-cyano-4,5-dihydrofuran (I) and 2-amino-3-cyano-5,6-dihydro-4H-pyran (II) from the sodium salt of malononitrile with



I n=1 III n=1
II n=2 IV n=2

2-bromoethanol and 3-bromopropanol, respectively. The dihydropyran derivative was of particular interest as an intermediate in the synthesis of α-cyano-δ-valerolactone (IV), a compound needed in an investigation of C—H acidity of lactones, and as a possible precursor in the synthesis of α-substituted δ-lactones.[2] A pronounced tendency for base catalysed cyclisation exists for γ- and δ-hydroxynitriles with activating α-substituents to give the stable enamine form of this type of iminolactones. The reported conversion of α-cyanolactones to 3-carbethoxy derivatives of 2-amino-dihydro-furans and pyrans [3] seems to be an expression of the same tendency. These facts, and the ease with which the enamines are hydrolysed to carbonyl compounds, make this route to α-cyanolactones an attractive one. Particularly in the case of δ-lactones the method is useful, since α-cyano-δ-lactones are not otherwise easily obtainable. α-Cyano-γ-lactones, on the other hand, are conveniently prepared from cyanoacetic ester with ethylene oxides.[4–6]

In the hydroxyalkylation of the sodium salt of malononitrile, 3-bromopropanol was much more reactive than 2-bromoethanol. The same phenomenon is observed in the reaction of these compounds with α-carbethoxy lactones,[2] and the low reactivity of 2-bromoethanol in malonic ester synthesis has been reported earlier.[7]

That the cyclic compounds (I) and (II) are present in the enamine and not in the imino form, can be seen from their strong ultraviolet absorption at about 225 mμ.[8] The low infrared stretching frequency of the cyano group at 2175 cm^{-1}, and the presence of three and four NMR absorptions of equal intensities for the compounds (I) and (II), respectively, can only be explained by the enamine structure.

Acid hydrolysis rapidly transformed the dihydrofuran (I) and the dihydropyran (II) derivatives to the α-cyano-γ- (III) and δ- (IV) lactones, respectively.

Experimental. 2-Amino-3-cyano-4,5-dihydrofuran (I). To finely divided sodium (7.8 g) in toluene (200 ml) and diethyl ether (200 ml) was added malononitrile (22 g) in ether (200 ml). The reaction mixture was heated to 50°, and dry ethanol (25 ml) added in small portions under stirring. When all the sodium was dissolved, 2-bromoethanol (42 g) was added dropwise, and the stirring continued for 12 h at 50°. After cooling, the reaction mixture was filtered, the solid matter washed with ether, and the solutions combined. The solvents were evaporated under reduced pressure, giving a yellowish, crystalline residue, which on recrystallisation from benzene gave almost colourless crystals (3.6 g, 10 %), m.p. 113—114°. (Found: C 54.76; H 5.52; N 25.20. Calc. for $C_5H_6N_2O$: C 54.54; H 5.49; N 25.49.) IR absorption bands ($CHCl_3$) were found at 3450, 3350, 2175, 1640, and 1580 cm^{-1}. NMR (DMSO-d_6) shifts were observed at

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δ 6.8 (broad), 4.33 (triplet), and 2.72 (triplet); the relative intensities were 1:1:1. UV absorption (MeOH) was found at 256 mμ (log ε 4.00).

2-Amino-3-cyano-5,6-dihydro-4H-pyran (II). Sodium (7.8 g) and malononitrile (22 g) gave with 3-bromopropanol (47 g) under the same conditions colourless crystals (21 g, 51 %), m.p. 107–108°. (Found: C 58.31; H 6.47; N 22.36. Calc. for $C_6H_8N_2O$: C 58.05; H 6.50; N 22.57). IR absorptions were located at 3450, 3350, 2175, 1630, and 1580 cm^{-1}, NMR (DMSO-d_6) signals at δ 6.0 (broad), 4.08 (triplet), 2.12 (triplet), and 1.8 (quintet) with relative intensities 1:1:1:1, and UV absorption at 254 mμ (log ε 3.83).

α-Cyano-γ-butyrolactone (III). A solution of 2-amino-3-cyano-4,5-dihydrofuran (I) (3.5 g) in 1 N sulphuric acid (60 ml) was kept at room temperature for 30 min. During this period it was extracted with ether at short intervals. The combined ether extracts were dried with sodium sulphate, and the solvent evaporated under reduced pressure. Distillation of the residue gave the lactone (1.4 g, 40 %), b.p.$_{10}$ 169–172°. The NMR and IR spectra were identical with those of an authentic sample, prepared by a different method.[4]

α-Cyano-δ-valerolactone (IV). Hydrolysis of 2-amino-3-cyano-5,6-dihydro-4H-pyran (II) (6 g) in 1 N sulphuric acid (100 ml) under the same conditions, afforded a colourless liquid (3.5 g, 55 %), b.p.$_{0.07}$ 128–130°, which crystallised within a few minutes, m.p. 51–52°. (Found: C 57.44; H 5.72; N 10.58. Calc. for $C_6H_7NO_2$: C 57.59; H 5.64; N 11.20). IR absorptions (KBr) were found at 2250 and 1730 cm^{-1}. NMR signals ($CDCl_3$) were located at δ 4.45 (triplet), 3.75 (four lines), and about 2.2 (multiplet); the relative intensities were 2:1:4. These data are consistent with the structure (IV).

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Bond-Bond Interactions in Organic Oxygen Compounds

Part III. Enthalpy of Formation of 2-(2-Methoxyethoxy)tetrahydropyran and the Contributory Group Increments

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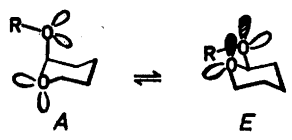
2-(2-Methoxyethoxy)tetrahydropyran (I) is a very suitable compound for a study of bond-bond interactions [1,2] since several increments including those due to oxygen atoms are involved.



(1)

I R = $CH_3OCH_2CH_2$–
II R = CH_3O–

One rabbit-ear effect [3–6] and one methyl-oxygen *gauche* interaction exist in the most stable rotamer of the equatorial conformer of 2-alkoxytetrahydropyrans (eqn. 1; E). Similarly, the most stable rotamer of the axial conformer (eqn. 1; A) is that in which two 1,3-diaxial hydrogen-oxygen interactions and one methyl-oxygen *gauche* interaction contribute.[6] The enthalpy difference between IA and IE (eqn. 1) is hence nearly equal to the difference between the enthalpy of interaction due to one rabbit-ear effect and that due to one axial alkoxy group. The latter interaction is obviously slightly greater than in methoxycyclohexane where $\Delta G°$ is 0.4 kcal/mole in favor of the equatorial conformation.[7] de Hoog and coworkers[8] have reported that the enthalpy difference between axial and equatorial conformers of 2-alkoxytetrahydropyrans is about 1.05 kcal/mole. If it is assumed that $\Delta H°$ for an axial alkoxy group in position 2 of tetrahydropyran is about 0.7 kcal/mole,