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RING SIZE LIMITATION IN 4-CHLORO-N-(o-HYDROXYPHENYL)BUTYRAMIDE CYCLIZATION.

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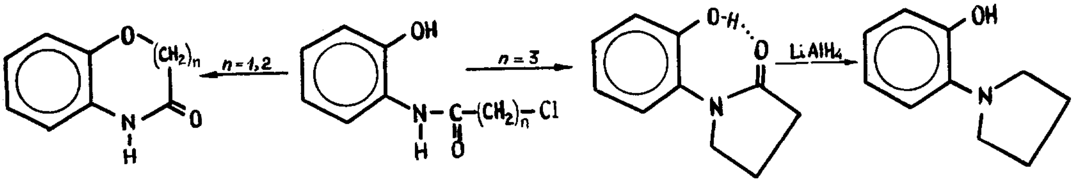
It is well known that in the presence of alkali bases the o-hydroxyphenyl-ω-chloroamides (I, n = 1, 2) produce the corresponding lactam (II, n = 1, 2) by an O-cyclization. (1,2) However, the sodium salt of 4-chloro-N-(o-hydroxyphenyl)butyramide (I, n = 3) leads to N-(o-hydroxyphenyl) 2-pyrrolidone (III) by a N^-- cyclization, and no trace of the attempted eight-membered lactame (II, n = 3) was isolated from the reaction mixture. The same compound (III), m.p. 135°, was also obtained in one step by heating 2-aminophenol with 4-chlorobutyryl chloride in the presence of triethylamine, and from sodium 2-aminophenoxide and γ-butyrolactone, in anhydrous conditions.



II I III IV

The structure assigned to the product thus obtained is supported by elemental analysis and the following spectral evidence :

The n.m.r. spectrum of compound III showed a low field singlet at 1.43 τ assigned to the hydroxyl proton, a complex pattern centered at 2.93 τ assigned to the aromatic protons, and three peaks for the methylene groups, which were located at 6.04 τ (triplet, J = 7 c.p.s.), at 7.38 τ (multiplet) and at 7.69 τ (multiplet).

The infrared spectrum of compound III shows a carbonyl absorption band at 1670 cm^{-1} which is slightly lower than that observed for other N-substituted 2-pyrrolidones. However, a broad absorption band in the 2600 - 3200 cm^{-1} region and no absorption band for any no-bonded O-H stretching vibration, even in very diluted carbon tetrachloride solutions, indicate an intramolecular hydrogen bond in III, which is responsible for the low value of the carbonyl absorption band. Furthermore, the spectra of some O-acyl-derivatives of III shows patterns with the amide I band shifted near 1700 cm^{-1} as in 2-pyrrolidone. (3).

By reduction with lithium aluminium hydride, the compound III afforded the known o-pyrrolidino-phenol (IV), m.p. 109°, (4), which was characterized as hydrochloride, m.p. 182° and p-nitrobenzoyl derivative, m.p.120.5°. The infrared and n.m.r. spectra of IV are in accord with recent literature data (5) and provided further evidence of the correctness of the structure assigned for the parent compound (III).

The different behaviour of the o-hydroxyphenyl-ω-chloroamides(I, n = 1,2,3) in the cyclization reactions shows that the relative importance of N- and O-attack may be governed by the sizes of the resulting rings. Taken in conjuction with Kornblum's generalization (6) about the alkylation of nucleophiles possessing two (or more) reaction sites, the preference for C-N oond formation might be an indication for the S_N2 character of the transition state.

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