A SHORT SYNTHESIS OF 3-OXO-1,2,3,4,5,6,7,8-OCTAHYDROISOQUINOLINE-1-SPIRO-1'-CYCLOHEXANE

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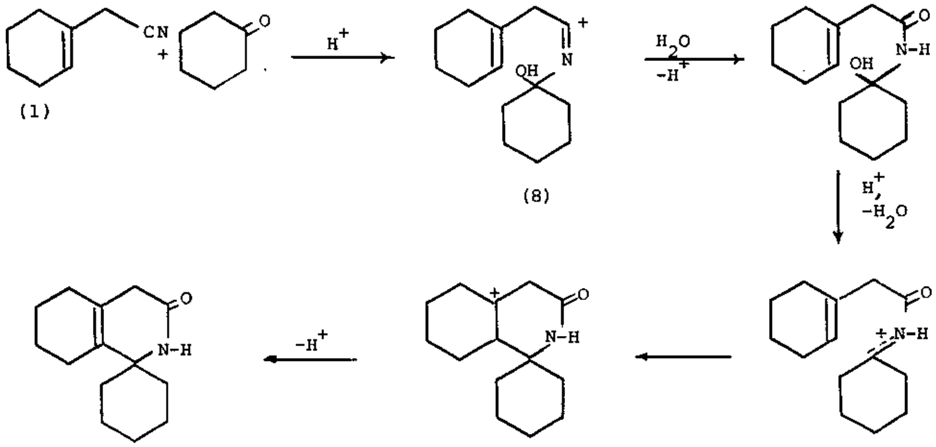
Abstract — Equimolar amounts of cyclohexanone and 1-cyclohexenylacetonitrile in polyphosphoric acid give 3-oxo-1,2,3,4,5,6,7,8-octahydroisoquinoline-1-spiro-1'-cyclohexane (4).

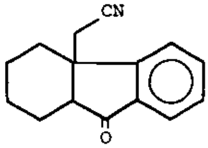
While investigating the potential application of substituted hexahydrofluorenones in syntheses of opium alkaloids[1] we found that reaction of 1-cyclohexenylacetonitrile (1) with benzoic anhydride in 83% polyphosphoric acid (PPA) did not give the desired cyanomethylhexahydrofluoren-9-one (2). However, we did obtain a small quantity of a compound, m.p. 215-217 °C, of molecular formula $C_{14}H_{21}NO$[2] the ^{1}H n.m.r. spectrum of which did not include signals attributable to aromatic protons. Accordingly, the reaction was repeated with the omission of benzoic anhydride, when a low yield of the same product was obtained, together with a 28% yield of the γ-lactone (3) arising from acid-catalysed hydrolysis of the nitrile (1) followed by cyclisation.[3] The origins of the new compound, and its molecular formula, suggested that its structure was either (4) or (5), and the i.r., u.v., and n.m.r. spectra allowed a clear distinction in favour of 3-oxo-1,2,3,4,5,6,7,8-octahydroisoquinoline-1-spiro-1'-cyclohexane (4).

Thus, in the SFORD ^{13}C n.m.r. spectrum the four resonances at lowest field were singlets; those at δ 170.0, and 131.4 and 124.4, were assigned to the carbon atoms of a lactam carbonyl group and of a tetrasubstituted double bond, respectively. The occurrence of the remaining singlet at δ 58.2 strongly suggested the presence of a quaternary carbon atom; an assignment which finds support in the reported[4] chemical shift (δ 59.6) for C-13 in compound (6). The remaining signals at δ 36.8, 34.8 (two carbon atoms), 29.7, 24.8, 24.3, 23.2, 22.5, and 21.0 (two carbon atoms) were all triplets and could be assigned readily to the methylene carbon atoms in compound (4). In particular the resonance at δ 36.8 allowed a clear distinction between the βγ-unsaturated lactam (4) and its isomer (5), since this signal due to a methylene carbon atom attached to a carbonyl group would be expected to occur near δ 31.0 in compound (5) [cf. δ 31.1 in (6),[4] and δ 31.5 in tetrahydro-2-pyridone[5]]. The infrared spectrum contained NH absorptions at 3 400 and 1 500 cm $^{-1}$ while the ^{1}H n.m.r. spectrum included a one-proton signal at δ 6.4 which disappeared on deuteriation. The carbonyl absorption at 1 650 cm^{-1} supported the six-membered βγ-unsaturated lactam (4),[6] since the analogous peak in the spectrum of the enamide (5) would be expected to be near 1 680 cm^{-1}.[7] Similarly, the position of the two-proton singlet at δ 2.82 is consistent with the expected chemical shift for methylene protons alpha to the carbonyl group in compound (4) (cf. δ 2.76 for compound (7)[8]) but is approximately δ 0.6 further downfield than would be anticipated for compound (5).[6] Finally, as expected for structure (4) the product showed no ultraviolet absorption maxima above 212 nm; cyclic enamides show quite strong absorption near 240 nm.[9,10]

On the premise that the lactam (4) was formed via condensation of 1-cyclohexenylacetonitrile with cyclohexanone (Scheme) equimolar amounts of these two compounds were heated together at 100 °C in 83% PPA for 15 min. The isolation of compound (4) in 42% yield confirmed this proposal.[11]



However, it is not clear whether in the initial experiments the cyclohexanone was generated from the nitrile (1) by a retro-aldol reaction, or was present as a trace impurity.[12] It is interesting that nitrilium ions like the proposed intermediate (8) have been shown recently to be key intermediates in a number of important classical organic reactions.[13]



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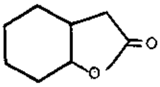

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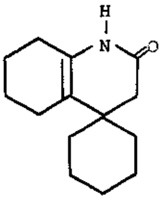

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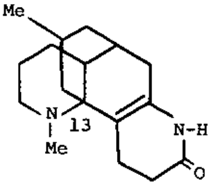

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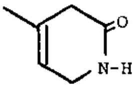

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