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A SYNTHESIS OF 1-SUBSTITUTED-3-HYDROXY-4,5-CYCLOALKYLPYRAZOLES

Neville Finch and Heinz W. Gschwend

Research Department, CIBA Pharmaceutical Company, Summit, N. J., 07901

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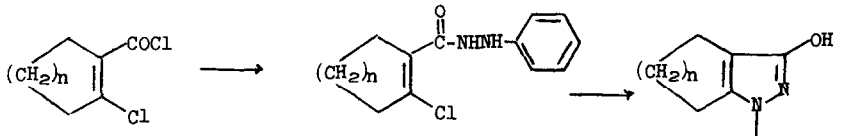
The preparation of 2-aryl(or alkyl)-3-hydroxytetrahydroindazoles is well known. As described nearly seventy years ago (1), condensation of ethyl 2-oxo-cyclohexanecarboxylate with phenylhydrazine leads exclusively to 2-phenyl-3-hydroxytetrahydroindazole I.

I

A general synthesis of the isomeric 1-aryl(or alkyl)-3-hydroxytetrahydroindazoles IV (n = 2) has, to our knowledge, not been described. We now report such a process.



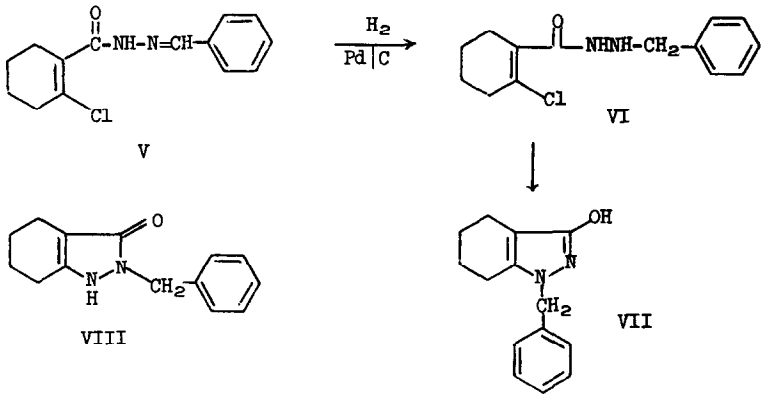
II III IV

The synthesis of compounds such as IV (n = 2) from ethyl 2-oxo-cyclohexanecarboxylate requires either an increased electrophilicity of the ester carbonyl and/or a less electrophilic carbonyl function. The ester carbonyl was activated by forming a mixed anhydride of 2-oxo-cyclohexanecarboxylic acid with ethyl chloroformate. However, condensation of this anhydride with phenylhydrazine again occurred first at the ketone carbonyl, thus

yielding I. 2-Chlorocyclohexene-1-carboxylic acid (2) corresponds to a starting material with a deactivated keto group. The acid chloride II (n = 2), in ether|methylene chloride at r.t., acylated phenylhydrazine on the more basic nitrogen. The phenylhydrazide III (n = 2) [m.p. 142°C, C=O ν_{max}^{Nujol} 1635(broad), 60% yield (3)] did not cyclize as readily as expected. It could be distilled unchanged at 170°|0.1 mm. Pyrolytic cyclization was effected only at temperatures in excess of 220°C. Preparatively, the cyclization was achieved by reflux in quinoline under nitrogen for two hours, or in naphthalene or diphenylether with 1-2 equivalents of quinoline. The reaction mixture was diluted with ether and the enolic product IV (n = 2) extracted by 1 N NaOH. Neutralization, extraction by methylene chloride and recrystallization from ethanol gave IV (n = 2) [53% yield, m.p. 207°C, ν_{max}^{Nujol} 1615 w, 1600 m, 1540 s, 1512 s; λ_{max}^{MeOH} 268 mμ (15,400)], whose spectral properties differed markedly from those of I [ν_{max}^{Nujol} 1640 m, λ_{max}^{MeOH} 248 mμ (14,000), 272 mμ (9,800)]. The tautomerism of I has been commented upon (4), and that of related compounds (5), however, IV exists almost exclusively in the enolic form, like other 1-substituted 3-hydroxy pyrazoles (6).

The method has generality, and substituted phenylhydrazides III can be cyclized in an analogous manner. Cycloheptapyrazoles IV (n = 3) have also been obtained, however, cyclopentapyrazoles IV (n = 1) are formed in low yield (10-20%). This is not too surprising, taking into account the high strain in this molecule, and the report (7) that the phenylhydrazone of ethyl 2-oxo-cyclopentanecarboxylate does not undergo cyclization.

Acylation of benzylhydrazine with II (n = 2) occurred mainly at the secondary nitrogen. When this mixture of hydrazides was subjected to the cyclization conditions, the undesired isomer VIII was the only isolatable product. VIII could also be obtained directly from ethyl 2-oxo-cyclohexanecarboxylate and benzylhydrazine. In order to extend the generality of the method to 1 alkyl derivatives, an alternate route to the appropriate acyl hydrazides was devised. Acylation of freshly distilled benzaldehyde hydrazone in methylenechloride with one equivalent of II (n = 2) and one equivalent of triethylamine gave V. (85% yield, m.p. 168°C, ν_{max}^{Nujol} 3170 w, 3070 m, 1660 s).



Controlled hydrogenation of the hydrochloride of V in ethanol over 10% Pd|C occurred swiftly and gave the benzylhydrazide VI (90% yield, m.p. 104°C, ν_{max}^{Nujol} 1630 s). Cyclization in refluxing quinoline yielded VII [35% yield, m.p. 182°C, ν_{max}^{Nujol} 2700-2500 broad, 1600 w, 1530 s, 1509 s; λ_{max}^{MeOH} 234 mμ (6,600), 258 mμ (3200)], whose spectral properties differed significantly from those of the isomer VIII.

Acknowledgment

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