NUCLEOPHILIC REACTIONS OF 5,6-DIHYDRONICOTINIC ACID ESTERS AND A NOVEL METHOD FOR THE PREPARATION OF 1,4,5,6-TETRAHYDROPYRIDINE-3-CARBOXYLIC ACID ESTERS

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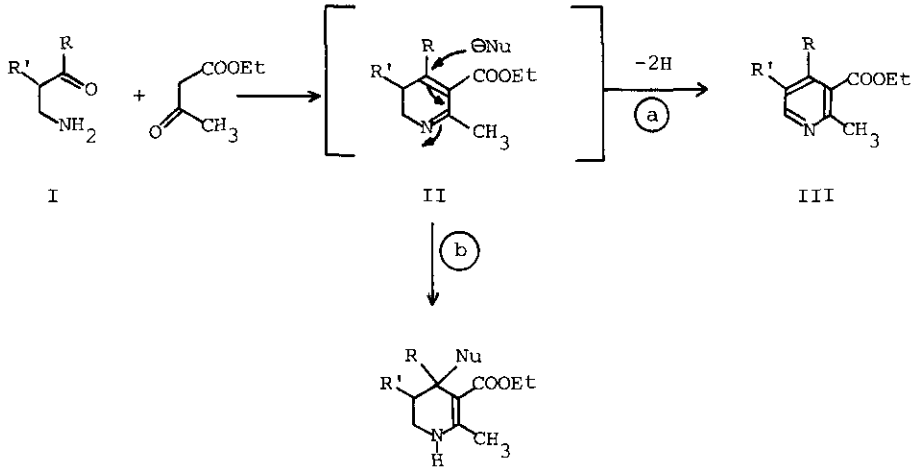
Reaction of 1,5-diaminopentan-3-one V with ethyl acetoacetate yielded diazaspiro-undecadiene-dicarboxylic acid ester VI by a one-step synthesis. Novel 4-aroyl-1,4,5,6-tetrahydropyridine-3-carboxylic acid esters XI and condensed analogs XIII have been prepared by cycloaddition of ethyl acetoacetate to α-methylene-β-amino-propiophenones or their cyclized analogs respectively.

With the exception of a single dihydropyrimidine derivative described by Gabriel[1], the primary β-aminoketones have attracted little attention as potential intermediates in the synthesis of heterocycles, even though β-aminoketones I became readily available by a procedure[2] first applied to the synthesis of kynuramine[3]. We have therefore investigated the condensation of I with ethyl acetoacetate and found that it results in the formation of substituted nicotinic acid esters III[2]. Presumably, 5,6-dihydronicotinic acid esters II are formed as intermediates in a first step.

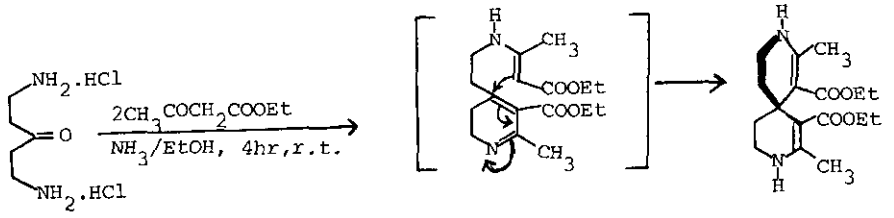
The work reported in this paper started with investigations aimed at demonstrating the intermediate formation of II through the addition of a nucleophile, possibly generating a 4,4-di-substituted tetrahydropyridine-3-carboxylic acid ester IV as a final product (scheme 1, (b)).



Scheme 1

In a first series of experiments, we tried to trap intermediate II by means of an external nucleophile, e.g. CN^-. At least after reaction of I, R= phenyl, R'=H, with ethyl acetoacetate in the presence of excess sodium cyanide, no trace of adduct IV could be isolated. Instead, dehydrogenation leading to the formation of the pyridine derivative III was the preferred secondary reaction.

Nevertheless, it was possible to demonstrate the feasibility of reaction type (b), scheme 1, when the presence of an internal nucleophilic center in intermediate II allowed an intramolecular addition. This is the case when 1,5-diamino-pentan-3-one V[4] is reacted with 2 moles of ethyl acetoacetate. In the presence of ammonia to prevent decomposition of the rather unstable free base of V, this reaction gave diaza-spiro-undecadiene-dicarboxylic acid ester VI (from MeOH hexagonal plates, mp 188-190°C) in a fairly good yield (67%), according to scheme 2.

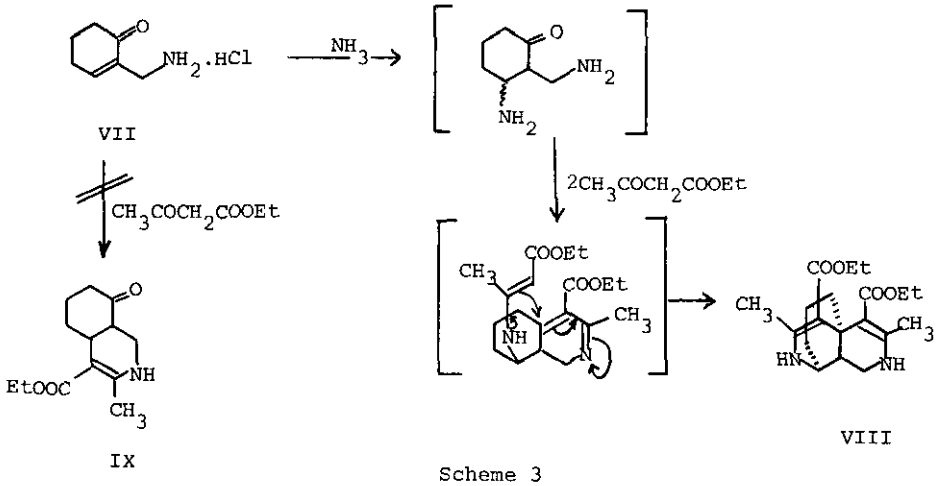


V VI

Scheme 2

Structure VI was confirmed by elementary analysis and the following spectral data: UV λ_{max}^{MeOH} nm (log ε): 287 (4.49); ir ν max (CH_2Cl_2): 3430 (NH), 1660 cm^{-1} (CO); nmr δ ($CDCl_3$) 1.09 (2x3H,t,OCH_2-$\underline{CH_3}$), 1.58/2.20 (2x2H,m,N-$CH_2\underline{CH_2}$-); 2.05 (2x3H,s,CH_3), 2.8-3.3 (2x2H,m,N-$\underline{CH_2}$) 3.77 (2x2H,q,OCH_2-), 6.05 (2x1H,sb,NH); ms $^m/e$ 322 (M^+), 277, 249, 203, 180, 164.

As a product of an analogous cyclization, the bridged 2,7-naphthyridine derivative VIII (mp 230-232°C) was isolated in a moderate yield from the complex reaction mixture obtained after dissolving the crude hydrochloride of 2-aminomethyl-cyclohexen-2-yl-ketone VII[5] and excess ethyl acetoacetate in ethanol saturated with ammonia. No other definite product could be isolated following chromatography of the crude product. Prior to cyclization, addition of ammonia to the α,β-unsaturated ketone VII presumably occurred, facilitating a double ring closure of the intermediate diaminoketone by condensation with ethyl acetoacetate, according to scheme 3.

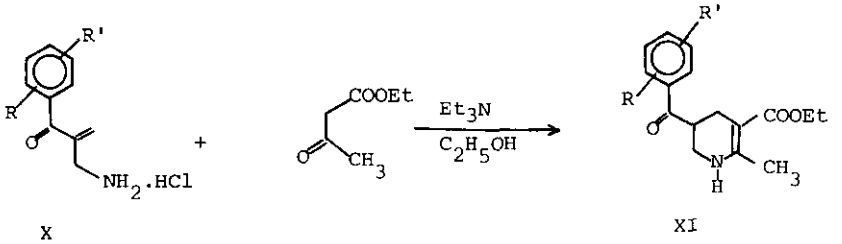


Scheme 3

Structure VIII was confirmed by elementary analysis and the following spectral data: ir νmax (KBr): 3250 (NH), 1660 cm^{-1} (CO); nmr δ(CD_3SOCD_3) 1.02 (3H,t, $OCH_2\underline{CH_3}$); 1.07 (3H,t,$OCH_2\underline{CH_3}$); 1.0-2.0(7H,m,$-CH_2-CH_2-CH_2-$,>C-H); 1.99(3H,s,=$\underline{CH_3}$); 2.12 (3H,s, =$\underline{CH_3}$); 2.75 and 3.12(2 and 1H,m, N-$CH_2$and N-CH); 3.85(2x2H,m,$2OCH_2$); 6.40(1H,sb,NH); 6.55(1H,d,NH); ms $^m/_e$ 348(M^+), 303, 274, 220, 146.

An alternative cyclization of VII could also have been taken place with one mole ethyl acetoacetate producing the oxo-octahydro-isoquinoline derivative IX by internal Michael-addition. However there was no evidence of this reaction having occurred.

On the other hand, the last-mentioned type of cyclization is preferred when α-methylene-β-aminopropiophenones X in the presence of a base are allowed to react with acetoacetic acid ester (scheme 4)



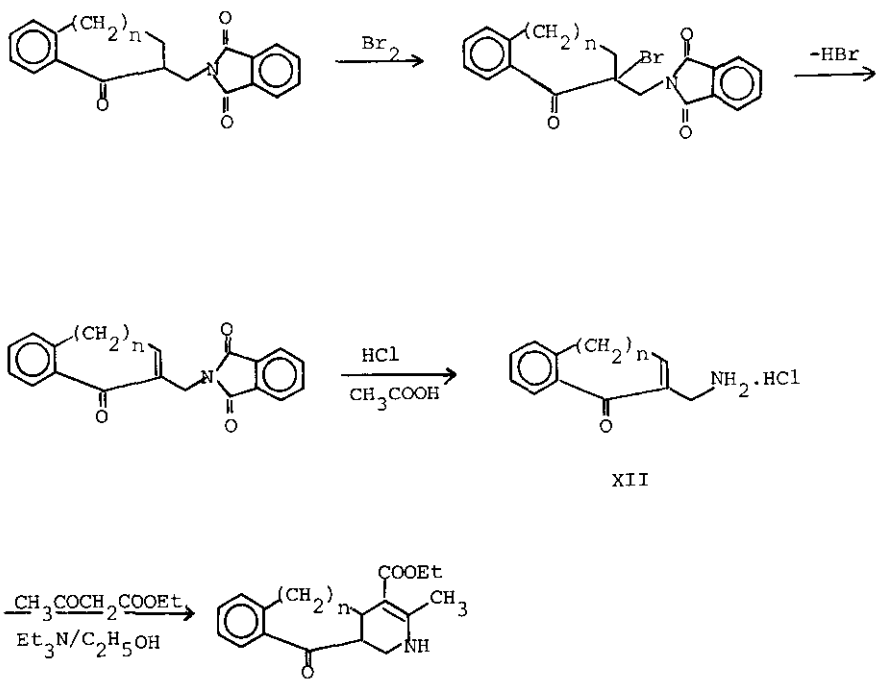
X XI

Scheme 4

In a typical experiment, for preparing XI (R,R'=2,6-dichloro), a solution of 65g (0.244 M) of crude 2,6-dichloro-α-methylene-β-aminopropiophenon-hydrochloride[6] in 250 ml ethanol was slowly added at room temperature to a solution of 65 ml ethyl acetoacetate (0.5 M) and 75 ml triethyl-amine in 200 ml ethanol. After being stirred for 14 hrs, the solution (containing a small amount of crystalline product) was concentrated in vacuo and diluted with 1 litre water, and the solid formed isolated by filtration, washed with water and ether and crystallized from acetic acid ethyl ester: yellow needles (42g,50%), mp 149-151°C, ir ν max (CH_2Cl_2) 3470 (NH), 1710 (CO), 1680 cm^{-1} (CO, ester); nmr δ($CDCl_3$) 1.21(3H,t,$OCH_2\underline{CH_3}$); 2.23(3H,s,=$\langle_{CH_3}$); 2.4-3.0 (2H,m,4-CH_2); 3.1-3.8(3H,m,5-CH and N-CH_2); 4.10 (2H,q,-O-CH_2); 4.35(1H,sb,NH); 7.32(3H,m,ar).

By essentially the same procedure XI, R,R'=H, mp 122-123° and XI, R=2-NO_2, R'=H, mp 125-127° have been prepared.

Furthermore, starting with cyclic arylketones the α,β-unsaturated aminomethylketones XII have been prepared according to scheme 5[7]. Their cyclization with ethyl acetoacetate by the procedure described above provided a novel access to the tetrahydropyrido-indanone-carboxylic acid ester XIII, n=0[8], mp 139-140° and likewise to the tetrahydropyrido-benzsuberone-carboxylic acid ester XIII, n=2[8], mp 121-122°C.



XII

XIII

Scheme 5

Thus the cycloaddition of ethyl acetoacetate to an α-amino-methyl acrylic moiety provides a versatile method for preparing substituted and condensed tetrahydropyridine derivatives, which may be useful intermediates in medicinal chemistry.

ACKNOWLEDGEMENT

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2 H. Zahn, Dissertation Univ. Munich, October 1957

3 A. Butenandt and U. Renner, Z. Naturforsch., 1953, 8b, 454

4 1,5-Diaminopentan-3-one dihydrochloride V was obtained by acid hydrolysis (HCl/glacial acetic acid at 130°C) of 1,5-diphthalimidopentan-3-one which was prepared from N-methyl-4-piperidone methiodide and potassium phthalimide in dimethylformamide.

5 2-Aminomethyl-cyclohexen-2-yl-ketone hydrochloride was prepared by bromination of 2-phthalimidomethyl-cyclohexanone[2], dehydrobromination of the 2-bromo-derivative using collidine and acid hydrolysis (HCl/CH_3COOH) of the 2-phthalimidomethyl-cyclohexen-2-one.

6 The α-methylene-β-aminopropiophenones are obtained by cleavage of the corresponding bis-phthalimidomethyl-acetophenones with HCl/CH_3COOH at 130°C.

7 2-Phthalimidomethyl-indanone and 2-phthalimidomethyl-benzsuberone have been prepared from the corresponding dimethylaminomethylketones by the procedure described in ref. 2.

8 The cis-configuration of these compounds is suggested by analysis of their nmr-spectra (360 MHz).

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