

55. The Reaction of Pyruvic Acid with Amines and Aminoesters Reexamined

Preliminary communication

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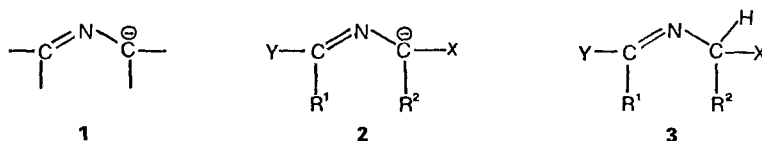
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Summary

Phenylglycine esters react with pyruvic acid to give α -methylsuccinic amides **9** instead of the expected *Schiff* bases **8**, analogously to *p*-anisidine but unlike aniline.

Aza-allylic carbanions (**1**) are considered important intermediates in organic synthesis²⁾, their generation however suffers from the general disadvantage that the bases used are rather sophisticated (alkali amides, organolithiums, alkali silylamides), difficult to handle in large scale preparations. Access to anions **1** might be possible using conventional bases (alkoxides) provided that electronwithdrawing groups X and/or Y are placed at the end of the aza-allylic chain (e.g. in **2**). Carboxy or carbalkoxy azomethines **3** (Y=COOH or COOAlk) respond to this

Scheme 1



requisite: they are *Schiff* bases derived from α -ketoacids (Y=COOH) or ketoesters (Y=COOAlk) and amines (X=H or alkyl) or α -aminoesters (X=COOAlk). Pyruvic acid *Schiff* bases have been only invoked as intermediates in transaminations [2], in the preparation of amino acids (*Knoop-Oesterlin* synthesis [3] and its extensions [4] or variations [5]), in the reaction of α -aminoesters with α -ketoesters [6], although they have been isolated either as pyruvamide imines [7] or in the form of cobalt coordination compounds [8].

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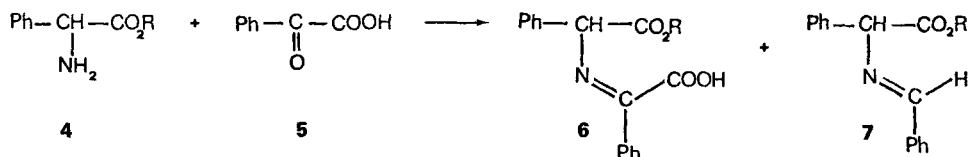
²⁾ References are necessary incomplete but [1] may serve as leading ones.

The reaction of α -aminoesters with pyruvic acid, expected to be a preparative entry to the corresponding azomethines on the basis of the large body of data just mentioned, surprisingly gave instead products of further condensation.

This communication is concerned with a few examples of the reaction of amines (aminoesters) with α -ketoacids.

Phenylglycine esters **4a** or **4b**³⁾ condense cleanly with phenylglyoxylic acid (**5**) (CH_2Cl_2 , room temp., two days) to give the *Schiff* bases **6** (**6a**: m.p. 106–108° (dec.); 76% [$^1\text{H-NMR.}$: 5.08 (CH)]; **6b**: m.p. 102–104° (dec.), 63% [$^1\text{H-NMR.}$: 5.21 (CH)]) together with smaller amounts of the corresponding decarboxylated products **7** (**7a**: oil [$^1\text{H-NMR.}$: 5.21 (CH), 8.3 (H–C=)]; **7b**: oil [$^1\text{H-NMR.}$: 5.25 (CH), 8.04 (H–C=)]). The *N*-benzalphenylglycine ethylester (**7b**) can in turn be obtained quantitatively by thermal decarboxylation in bulk at 110° of the acid **6b**⁴⁾. In this respect the acids **6** behave as aza-vinylogs of phenylmalonic acid monoesters.

Scheme 2



Work-up of the reaction mixture from equimolar amounts of pyruvic acid and racemic phenylglycine methyl (**4a**) or ethyl (**4b**) (in CH_2Cl_2 or ethyl ether, room temp., two days) did not give the expected azomethines **8** but led to isolation, as major components⁵⁾, of products which arise from the decarboxylative condensation of two pyruvic acid and two aminoester residues. Interpretation of ^1H - and ^{13}C -NMR. spectra suggested that the isolated products are diastereomeric mixtures of methylsuccinic amides of phenylglycine methyl (**9a**) and ethyl (**9b**) esters, respectively (**9a**, m.p. 150–152° (sint. 148°) from $\text{MeOH}/\text{H}_2\text{O}$, 153–155° from benzene, crude 40%, recryst. 30% [$^1\text{H-NMR.}$: 6.8–6.9 (NH); 5.45–5.55 (CH–NH); 3.3 (COOCH_3); 2–3 (ABC-System, HC-CH_2); 1.5 (CH_3); $^{13}\text{C-NMR.}$: 174.8 and 171.13 (CO); 136, 128.7, 128.3, and 127.2 (arom. C-atoms)]; 56.5 (CH–NH); 52.6 (COOCH_3); 39.6 (CH_2); 37.1 (CH); 13.6 (CH_3); MS.: m/e = 426; **9b**, m.p. 125–128°, 30% [$^1\text{H-NMR.}$: 6.85 and 6.95 (NH); 5.45 and 5.55 (CH); 4.15 (CH_2); 2–3 (ABC-System, CH-CH_2); 1.15 (CH_3); MS.: m/e = 454]).

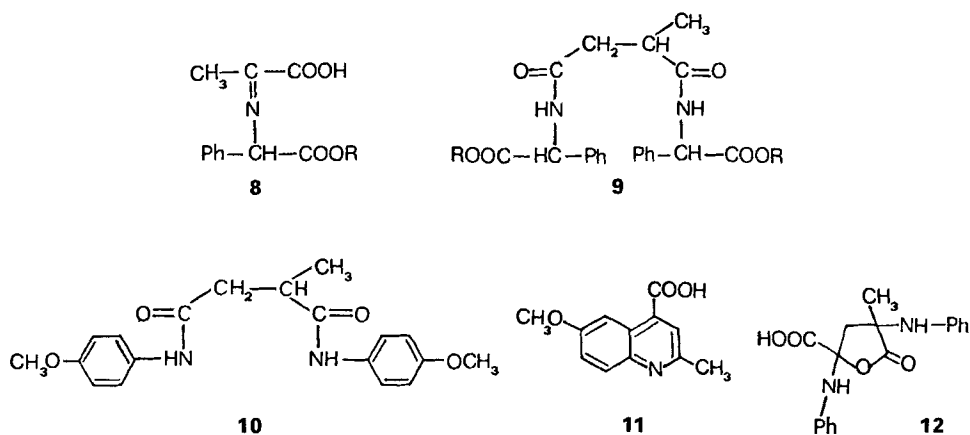
Structure **9a** for the obtained product was confirmed by independent synthesis: methylsuccinoyl dichloride [**9**] and racemic phenylglycine methyl ester (ratio 1:4, benzene, room temp., 60%) gave a compound (m.p. 158–160° (dec.)) which showed

³⁾ a: $\text{R} = \text{CH}_3$, b: $\text{R} = \text{C}_2\text{H}_5$.

⁴⁾ The acid ester **6a** undergoes decarboxylation also under much milder conditions (CH_2Cl_2 , reflux for 3 h, ca. 50%).

⁵⁾ Non-identified carboxylic acids are obtained as side products on washing the crude reaction mixture with NaHCO_3 -solution followed by careful acidification: their relative amount however increase when the pyruvic acid used is not freshly distilled.

Scheme 3



$^1\text{H-NMR}$. characteristics slightly different from those exhibited by the sample obtained from pyruvic acid. We attributed the slight differences in the two samples to a slightly different composition of their diastereomeric mixtures. It is apparent that in the condensation products **9** the C-atoms of the carbonyl functions originally present in pyruvic acid undergo a dismutation, one being formally reduced to a methine group (CH-CH_3), and the other being formally oxidized to the carbonyl group of one of the amide functions. An analogous dismutation of pyruvic acid has been reported over 70 years ago by *Giuffrida & Chimienti* [10], who allegedly obtained α -methylsuccinic di-*p*-aniside (**10**) on treating pyruvic acid with *p*-anisidine in ethanol. On repeating this reaction we have found that indeed, **10** (m.p. $241\text{--}242^\circ$) [$^1\text{H-NMR}$.: 9.8 (NH); 6.8–7.45 ($AA'BB'$ -System, arom. H); 3.7 (OCH_3); 2–3 (ABC -System, CH-CH_2); 1.25 (CH_3)] is formed in good yields both in methylene chloride and in ethyl ether while in ethanol the quinoline acid **11** [11] (m.p. $286\text{--}288^\circ$) (EtOH) [$^1\text{H-NMR}$.: 8.1 (*s*, H-C(3)); 8.73 (*d*, H-C(5)); 7.55 (*d* $\times$ *d*, H-C(7)); 8.2 (H-C(8)); 3.86 (*s*, OCH_3); 2.73 (*s*, CH_3)] is formed preferentially although in moderate yields.

Aminoesters **4** thus behave toward pyruvic acid analogously to *p*-anisidine but unlike aniline: in this case in fact the lactone **12** was isolated in high yields by *Wieland* [12]⁶).

The reaction of pyruvic acid with α -amino acids and thus also with α -amino esters is considerably relevant for its biological implications: failure of observing so far condensation products of type **9** under conditions for transamination and for amino acid synthesis is undoubtedly due to the fortunate interception of the intermediate *Schiff* bases of pyruvic acid either by prototropic equilibria or by

⁶) We checked also this reaction, both under *Wieland's* conditions in ether and under our conditions in CH_2Cl_2 : we isolated a compound (m.p. 123° lit. [12] m.p. 122°) whose $^1\text{H-NMR}$. spectrum is indeed in accord with structure **12** ($^1\text{H-NMR}$. (acetone- d_6): 1.57 (*s*, CH_3); 2.55 (AB -System, $J_{AB} = 12$ Hz, CH_2)), and which appears to be only one of the two possible diastereoisomers.

a reducing agent before they had chances of evolving any further. Under our and *Wieland's* conditions *Schiff* bases of pyruvic acid have such chances: their fate however appears to be determined by the solvent and by the basicity/nucleophilicity of the amine component.

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