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

Preliminary communication

by **Silvia Bradamante, Silvana Colombo, Giorgio A. Pagani**[1]) and **Stefano Roelens**

Centro CNR c/o Istituto di Chimica Industriale dell'Università, via Golgi 19, I-20133 Milano

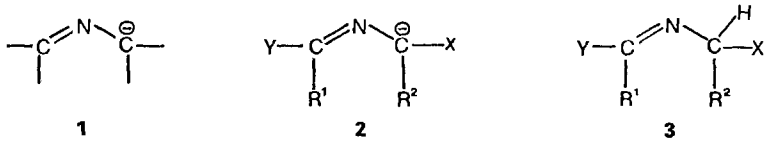
(6.II.81)

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 synthesis[2]), 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



1 **2** **3**

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 pyruvamides imines [7] or in the form of cobalt coordination compounds [8].

[1]) Author to whom correspondence should be addressed.

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

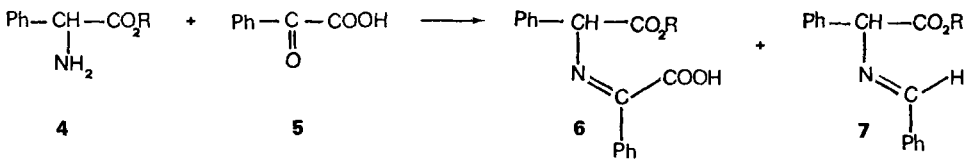
0018-019X/81/2/0568-04$01.00/0

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}H-NMR.: 5.08 (CH)]; **6b**: m.p. 102–104° (dec.), 63% [^{1}H-NMR.: 5.21 (CH)]) together with smaller amounts of the corresponding decarboxylated products **7** (**7a**: oil [^{1}H-NMR.: 5.21 (CH), 8.3 (H–C=)]; **7b**: oil [^{1}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 components[5]), of products which arise from the decarboxylative condensation of two pyruvic acid and two aminoester residues. Interpretation of ^{1}H- 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 MeOH/H_2O, 153–155° from benzene, crude 40%, recryst. 30% [^{1}H-NMR.: 6.8–6.9 (NH); 5.45–5.55 (C*H*–NH); 3.3 ($COOCH_3$); 2–3 (A*B*C-System, *H*C–CH_2); 1.5 (CH_3); ^{13}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}H-NMR.: 6.85 and 6.95 (NH); 5.45 and 5.55 (CH); 4.15 (CH_2); 2–3 (A*B*C-System, C*H*–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

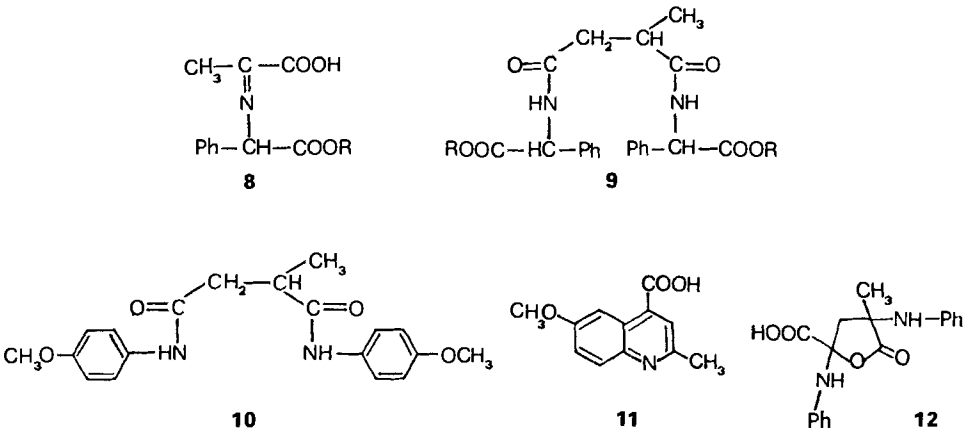
---

[3]) *a*: R = CH_3, *b*: R = C_2H_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



8 **9** **10** **11** **12**

^{1}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 alledgedly obtained α-methylsuccinic di-*p*-anisidide (**10**) on treating pyruvic acid with *p*-anisidine in ethanol. On repeating this reaction we have found that indeed, **10** (m.p. 241–242°) [^{1}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. 286–288°) (EtOH) [^{1}H-NMR.: 8.1 (*s*, H–C(3)); 8.73 (*d*, H–C(5)); 7.55 (*d*×*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}H-NMR. spectrum is indeed in accord with structure **12** (^{1}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.

REFERENCES

[1] a) *T. Kauffmann*, Angew. Chem. Int. Ed. *13*, 627 (1974); b) *G. Stork, A. Y. W. Leong & A. M. Tonzin*, J. Org. Chem. *41*, 3491 (1976); c) *J. J. Fitt & H. W. Gschwend*, J. Org. Chem. *42*, 2639 (1977); d) *P. Bey & J. P. Vevert*, Tetrahedron Lett. *1977*, 1455; e) *S-i. Yamada, T. Oguri & T. Shioiri*, Chem. Commun. *1976*, 136; f) *M. J. O'Donnell & T. M. Eckrich*, Tetrahedron Lett. *1978*, 4625; g) *M. J. O'Donnell, J. M. Boniece & S. E. Earp*, Tetrahedron Lett. *1978*, 2641; h) *R. R. Fraser, J. Banville & K. L. Dhawan*, J. Am. Chem. Soc. *100*, 7999 (1978) and references cited therein; i) *D. Savoia, C. Trombini & A. Umani Ronchi*, J. Org. Chem. *43*, 2907 (1978).

[2] a) *R. M. Herbst*, J. Am. Chem. Soc. *58*, 2239 (1936); b) *A. Schonberg, R. Moubasher & A. Mostafa*, J. Chem. Soc. *1948*, 176; c) *T. Wieland*, Angew. Chem. *55*, 147 (1942).

[3] *F. Knoop & H. Oesterlin*, Z. Physiol. Chem. *148*, 294 (1925).

[4] a) *R. G. Hiskey & R. C. Northrop*, J. Am. Chem. Soc. *87*, 753 (1965); b) *K. Harada & K. Matsumoto*, J. Org. Chem. *33*, 4467 (1968) and previous papers; c) *K. Harada, T. Iwasaki & T. Okawara*, Bull. Chem. Soc. Jpn. *46*, 1901 (1973); d) *S-i. Yamada & S-i. Hashimoto*, Tetrahedron Lett. *1976*, 997.

[5] a) *S-i. Yamada & S-i. Hashimoto*, Chem. Lett. *1976*, 921; b) *N. Takaishi, H. Imai, C. A. Bertel & J. K. Stille*, J. Am. Chem. Soc. *98*, 5401 (1976).

[6] *S. D. Brewer & R. M. Herbst*, J. Am. Chem. Soc. *63*, 867 (1941).

[7] *W. Lopatin, P. R. Young & T. C. Owen*, J. Am. Chem. Soc. *101*, 960 (1979) and previous papers.

[8] *J. Mac B. Harrowfield & A. M. Sargeson*, J. Am. Chem. Soc. *101*, 1514 (1979).

[9] *G. F. Morrell*, J. Chem. Soc. *105*, 1733 (1914).

[10] *G. Giuffrida & A. Chimienti*, Gazz. Chim. Ital. *34*, 261 (1904).

[11] *J. Halberkann*, Ber. Deutsch. Chem. Ges. *54*, 3104 (1921).

[12] *T. Wieland, G. Omacker & R. K. Rothhaupt*, Chem. Ber. *88*, 633 (1955).