Notes

A department for short papers of immediate interest.

Action of Grignard Solutions on 2-Acyl-1,2-benzisothiazol-3(2*H*)-one 1,1-Dioxide

WAFIA ASKER, AHMED MUSTAFA, MUSTAFA KAMAL HILMY, AND MOHAMED ALY ALLAM

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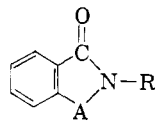
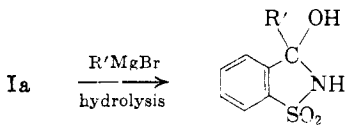
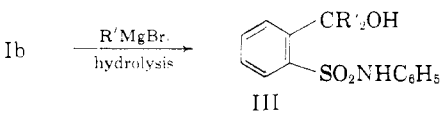
Recently, Mustafa and co-workers[1] have studied the reaction of organomagnesium compounds with *N*-substituted-1,2-benzisothiazol-3(2*H*)-ones (*e.g.*, Ia and Ib) and related dioxides (*e.g.*, Ie and If). It was found that addition of phenylmagnesium bromide to Ia,b,e,f, led to the formation of IIc, III, IV, and V, with ring cleavage occurring in two instances.



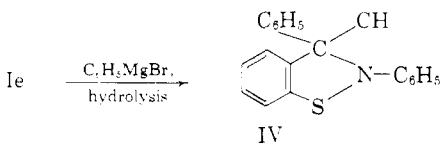
Ia, A = SO_2; R = H
b, A = SO_2; R = C_6H_5
c, A = SO_2; R = $COCH_3$
d, A = SO_2; R = COC_6H_5
e, A = S; R = C_6H_5
f, A = S; R = $SO_2C_6H_5$



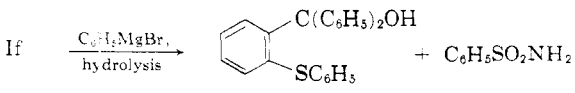
IIa, R′ = CH_3
b, R′ = C_2H_5
c, R′ = C_6H_5



III



IV



We have now investigated the reaction of Grignard reagents with *N*-acyl-1,2-benzisothiazol-3-(2*H*)-one 1,1-dioxides (Ic,Id) to see what the effect of acyl substitution is on addition and on ring cleavage. We found that phenylmagnesium bromide, ethylmagnesium iodide, and methylmagnesium iodide add to the hetero carbonyl group as expected, accompanied by removal of the acyl group.[2]

EXPERIMENTAL

Behavior of Id, Ic, and/or Ia toward: (a) *Phenylmagnesium bromide.* The following exemplifies the procedure. To a Grignard solution (prepared from 0.9 g. of magnesium and 9 g. of bromobenzene in 50 ml. of dry ether) was added a solution of 1 g. of each of Id, Ic, and/or Ia in dry benzene (30, 40, and 60 ml., respectively). The water was removed from the reflux condenser and the ether evaporated from the reaction mixture, which was then heated for 6 hr. on a steam bath. After standing overnight at room temperature, it was poured slowly into 100 ml. of saturated aqueous ammonium chloride solution containing a few ml. of concentrated hydrochloric acid and extracted with ether. The ether benzene mixture was dried and evaporated. The solid residue so obtained was washed with cold light petroleum (50 ml.) and extracted with hot petroleum ether (80–100°). Crystallization of the insoluble part from toluene gave 0.5 g., 0.46 g., and 0.78 g. of IIc,[3] respectively (m.p. 192°; melting point and mixed melting point determination and color reaction with concentrated sulfuric acid).

Anal. Calcd. for $C_{13}H_{11}O_3SN$: C, 59.77; H, 4.21; S, 12.26; N, 5.36. Found: C, 59.46; H, 4.19; S, 12.08; N, 5.21.

Working up of the petroleum ether extracts gave 0.28 g. of triphenylcarbinol and 0.2 g. of diphenylmethylcarbinol[4] in case of Id and Ic respectively.

(b) *Ethylmagnesium iodide.* Similarly, treatment of 1 g. of Id, Ic, and/or Ia with ethylmagnesium iodide (prepared from 1.2 g. of magnesium and 10 g. of ethyl iodide in 40 ml. of dry ether) as described above gave 0.45 g., 0.5 g., and 0.82 g., respectively of colorless crystals from benzene light petroleum ether mixture, m.p. 131–132°; identified as IIb.

(c) *Methylmagnesium iodide.* Similar treatment with methylmagnesium iodide gave colorless crystals from ben-

(1) (a) A. Mustafa and M. K. Hilmy, *J. Chem. Soc.*, 1339 (1952); (b) A. Mustafa and O. H. Hishmat, *J. Am. Chem. Soc.*, **75**, 4647 (1953); (c) A. Mustafa and W. Asker and co-workers, *J. Am. Chem. Soc.*, **76**, 5447 (1954).

(2) The ready elimination of the acyl group by the action of Grignard solutions may be compared with the elimination of the benzoyl group in *N*-benzoyl phthalimide by the action of phenylmagnesium bromide (*cf.* A. Mustafa, W. Asker, and O. H. Hishmat, *J. Am. Chem. Soc.*, **77**, 5127 (1955). Ia, the imide of *o*-sulfobenzoic acid, may be viewed as a model of phthalimide having the sulfone group instead of the carbonyl group. Thus, it is not striking that the hetero ring in Ia is not cleaved [*cf.*, the stability of the hetero ring in phthalimide, C. Beis, *Compt. rend.*, **143**, 432 (1906)] and readily undergoes elimination of the acyl group by the action of phenylmagnesium bromide (*cf.*, the action of the same reagent on *N*-Benzoyl phthalimide, A. Mustafa, W. Asker and O. H. Hishmat loc. cit.).

(3) B. Oddo and Mingoia [*Gazz. chim. ital.*, **57**, 465 (1927)] have reported m.p. 185°, 119–120°, 110–111° for IIc, IIb, and IIa, respectively (see below).

(4) Identification was carried out by melting point and mixed melting point [*cf.* A. Klages, *Ber.*, **35**, 2646 (1902)] and the formation of red color with concentrated sulfuric acid.

zene light petroleum ether mixture, m.p. 129°; identified as IIa.

CHEMISTRY DEPARTMENT
FACULTY OF SCIENCE
CAIRO UNIVERSITY
GIZA, CAIRO, EGYPT

Syntheses of Poly-β-aspartyl Dipeptides

ALBERT ZILKHA

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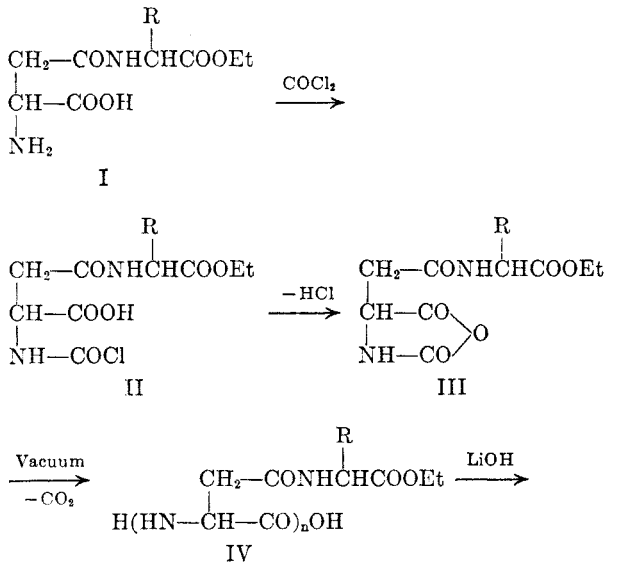
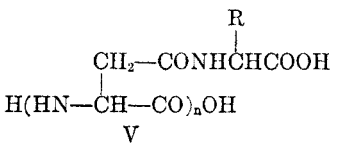
In continuation of previous work[1] on the polymerization of trifunctional amino acids, polyaspartic acids having their β-carboxyl group linked to other amino acids in a peptide linkage were prepared. These polymers are interesting in that they have a dipeptide linked to the backbone of a polymeric amino acid.

These polymers were prepared according to the accompanying scheme starting with DL-β-aspartyl-dipeptide ethyl esters (I) prepared by the maleic anhydride method[2] previously described. Passing phosgene into a suspension of these compounds in dioxane yielded their *N*-carboxy anhydride (III) probably through the intermediate *N*-chloroformyl derivatives (II), which were polymerized by heating *in vacuo*. The resulting poly-DL-β-aspartyl dipeptide



esters (IV) yielded the poly free dipeptides (V) on mild hydrolysis with lithium hydroxide (1*N*).



The polymers thus prepared included poly-DL-β-aspartylglycine, poly-DL-β-aspartyl-DL-alanine, poly-DL-β-aspartyl-DL-valine, poly-DL-β-aspartyl-DL-phenylalanine.

The poly dipeptides differed from the poly dipeptide esters in having much higher melting points and being more soluble in water and less in ethanol and other organic solvents. Their R_f-values were also much lower. They gave positive biuret reaction and positive ninhydrine after prolonged boiling.

Total hydrolysis of poly-DL-β-aspartylglycine ethyl ester was accomplished by refluxing the polymer in hydrochloric acid (5*N*) for 20 hr. This was confirmed by α-amino nitrogen determinations on the hydrolysate and paper partition chromatography whereby the characteristic spots of aspartic acid and glycine were obtained.

EXPERIMENTAL

Micro analyses are by Drs. Weiler and Strauss.

In the following a general description is given for the preparation of the *N*-carboxy anhydrides, poly-β-aspartyl dipeptide esters, and poly-β-aspartyl dipeptides, the specific polymers and their properties being tabulated in the accompanying table.

Preparation of N-carboxy anhydrides of DL-β-*aspartyl dipeptide ethyl esters.* To a suspension of 2 g. DL-β-aspartyl dipeptide ethyl ester, previously dried in a vacuum desiccator, in 100 ml. dry dioxane placed in a three-necked flask fitted with a mechanical stirrer, gas leading tube, and reflux condenser protected with a calcium chloride tube, phosgene dried over concentrated sulfuric acid was passed for 1 hr. at 60°. The substance dissolved during reaction. The solution was evaporated *in vacuo* at 40°, and the *N*-carboxy anhydride remained as a viscous oil which refused to crystallize.

*Poly-*DL-β-*aspartyl-dipeptide ethyl esters.* The *N*-carboxy anhydride was heated in a high vacuum system. At 60° there was gas evolution which stopped and started once more at about 80°. The heating was continued and the temperature allowed to reach 110–120°, after 2 hr. On cooling the polymer solidified.

*Poly-*DL-β-*aspartyl-dipeptides.* Poly-DL-β-aspartyl dipeptide ester (0.2 g.) was dissolved in 3 ml. lithium hydroxide (1*N*) and left for 2–3 hr. at room temperature. Where the polymer was insoluble in water, ethanol was added to effect solution. The solution was acidified with hydrochloric acid and evaporated to dryness *in vacuo*, leaving, sometimes, an oily residue which crystallized on addition of absolute ethanol. The polymer was filtered and washed with absolute ethanol to remove lithium chloride; water insoluble polymers were washed with this solvent. Only slight hydrolysis of the peptide linkages occurred under these conditions.

DEPARTMENT OF ORGANIC CHEMISTRY
THE HEBREW UNIVERSITY
JERUSALEM, ISRAEL

(1) M. Frankel and A. Berger, *Nature*, **163**, 213 (1949); *J. Org. Chem.* **16**, 1513 (1951); M. Frankel, M. Breuer, and S. Cordova, *Experientia VIII*, 299 (1942); *J. Chem. Soc.*, 1991 (1953); M. Frankel, M. Harnik, Y. Levin, and Y. Knobler, *J. Am. Chem. Soc.*, **75**, 78 (1953); E. Katchalski, I. Grossfeld, and M. Frankel, *J. Am. Chem. Soc.*, **69**, 2564 (1947); **70**, 2094 (1948). M. Frankel, Y. Liwschitz, and A. Zilkha, *J. Am. Chem. Soc.*, **75**, 3270 (1953).

(2) Y. Liwschitz and A. Zilkha, *J. Am. Chem. Soc.*, **77**, 1265 (1955).