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HOFMANN DEGRADATION AND BROMINATION OF AMIDES DERIVED FROM PHOSPHONOACETIC ACID

Mirosław Soroka and Przemysław Mastalerz

Institute of Organic and Physical Chemistry, Technical University of Wrocław, Poland

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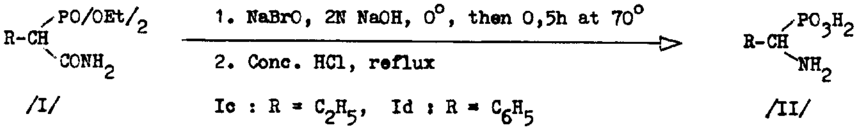
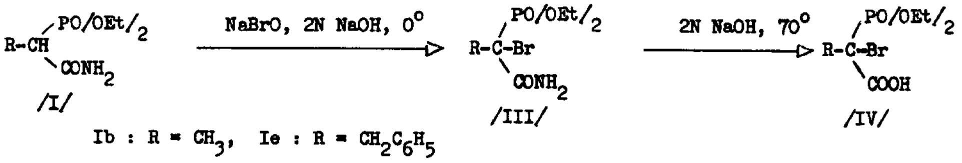
Isbell et al. described recently the synthesis of a variety of 1-aminophosphonic acids/II/ by Curtius degradation of C-substituted esters of phosphonoacetic acid.[1,2] No other method to prepare II from phosphonoacetic acid derivatives has been reported so far.

Continuing our studies on the synthesis of biologically interesting aminophosphonic acids,[3,4] we turned our attention to the Hofmann degradation of amides /I/ derived from phosphonoacetic acid as a possible route to II. This approach appeared to be promising because 1-aminocarboxylic acids have been prepared[5] by Hofmann degradation of monosubstituted malonamic esters analogous to I.



However, under the conditions typical for Hofmann degradation, e.g. using alkaline NaBrO, the amides /I/ might be expected also to undergo a bromination at the carbon atom, although no such reaction had been observed in the malonamic acid series.[5]

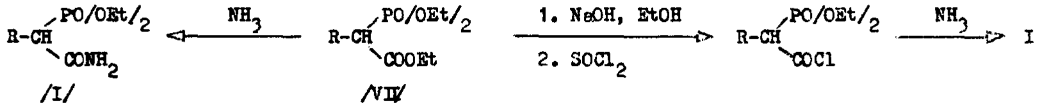


Our results obtained with 5 amides /I/ demonstrate that the reaction depends very much upon the structure of the radical R. With R being ethyl or phenyl virtually no bromination was observed and the corresponding aminophosphonic acids[6] were isolated in 70-80% yield. With R = H /Ia/ no trace of aminomethylphosphonic acid could be detected in the reaction mixture after hydrolysis and the only products were diethylphosphonodibromoacetamide /V, m.p. 91-2°/ and diethylphosphonodibromoacetic acid /VI, m.p. 90-2°/.The isolated yield of /V/ increased to 75% when two moles of NaBrO were used in the reaction instead of one mole as usual in Hofmann degradation.Bromination was also practically the only reaction with Ib although traces of IIb were detectable chromatographically after acid hydrolysis. The actually isolated product /IVb, m.p. 109-12°/ was obtained in 70% yield.In the case of Ie, the brominated amide /IIIe, m.p. 87-9°/ was isolated in 80% yield and there was no observable Hofmann degradation.

The reactions were performed by adding 0,1 mole of amide dissolved in 30 ml of cold water to NaBrO solution prepared freshly from 0,105 mole of Br_2, 0,6 mole of NaOH and 170g of ice and water. The temperature was kept at 0° during the amide addition and was than raised to 70° for 0,5h. Heating was avoided in experiments where brominated amides were isolated. The reaction mixtures were worked up by acidification to pH=1 with HCl and extraction of brominated amides /III/ or acids /IV/ with ether or CH_2Cl_2.Aminophosphonic acids were isolated from the water layers using standard procedures after hydrolysis with conc. HCl. The reactions with NaBrO were carried out under identical conditions in all cases.

The results indicate that the effect of structure on the reaction of amides /I/ with NaBrO is quite dramatic. Particularly surprising are the profound and opposite effects of chain lengthening by one CH_2 group exemplified by the behaviour of Ic compared with Ib and of Ie compared with Id. Additional studies, including more structural variations, are needed to explain these phenomena.

The starting amides /I/ were prepared from corresponding esters /VII/ by ammonolysis /method A/ or by partial alkaline hydrolysis followed by successive treatment with $SOCl_2$ and NH_3 /method B/.



$$\underset{/I/}{R\text{-}CH\begin{matrix}\nearrow PO/OEt/_2\\ \searrow CONH_2\end{matrix}} \xleftarrow{NH_3} \underset{/VII/}{R\text{-}CH\begin{matrix}\nearrow PO/OEt/_2\\ \searrow COOEt\end{matrix}} \xrightarrow[2.\ SOCl_2]{1.\ NaOH,\ EtOH} R\text{-}CH\begin{matrix}\nearrow PO/OEt/_2\\ \searrow COCl\end{matrix} \xrightarrow{NH_3} I$$

Data concerning the synthesis of previously unreported amides /I/ are as follows /m.p., yield and method are indicated/ : Ib, 62-5°, 75% A, 65% B; Ic, 100-2°, 85% A, 70% B; Id, 167-9°, 90% A, 80% B; Ie, 76-8°, 75% A, 65% B. The synthesis of amides /I/ was attempted also by alkylation of the amide /Ia/ but the results were disappointing.

References and Footnotes

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6. The structures of all isolated compounds were confirmed by elemental analysis, IR and NMR spectra or by comparison with authentic samples prepared by independent procedures.