Chem. Ber. 112, 148–160 (1979)

Syntheses of DL-Serine and of Precursors thereof (Glycolaldehyde and "Masked" Glycolaldehydes)

Luciano Bassignani, Bruno Biancini, Alberto Brandt, Valerio Caciagli, Giancarlo Eletti Bianchi, Luciano Re, Antonio Rossodivita,* and *Piergiorgio Zappelli*

Snamprogetti S.p.A., L.P.M., Via Ercole Ramarini 32, Monterotondo (Rome), Italy

Received, 9th March, 1978

On treatment of vinyl chloride epoxide (**4**) with water, of chloroethylene carbonate (**9**) with aqueous bases, of vinyl acetate (**1**) or ethyl vinyl ether (**6**) with aqueous potassium chlorate and catalytic amounts of osmium tetroxide, glycolaldehyde (**5**) was formed (scheme 1). The not isolated aldehyde **5**, when submitted to the *Zelinsky-Stadnikoff* amino acid synthesis, afforded DL-serine in 70% yield. The latter method, when applied directly to the "masked" glycolaldehydes **2**, **7**, **9**, **10**, vinylene carbonate (**11**), **13** or **14**, also gave DL-serine (yields 35–70%), whereas with **4** no serine formation could be detected (scheme 1).

Synthesen von DL-Serin und Vorläufern (Glycolaldehyd und „maskierte" Glycolaldehyde)

Bei Behandlung von Vinylchloridepoxid (**4**) mit Wasser, von Chlorethylencarbonat (**9**) mit wäßrigen Basen, von Vinylacetat (**1**) oder Ethylvinylether (**6**) mit wäßrigem Kaliumchlorat und einer katalytischen Menge Osmiumtetroxid bildete sich Glycolaldehyd (**5**) (Schema 1). Der nicht isolierte Aldehyd **5** lieferte bei der *Zelinsky-Stadnikoff*-Aminosäure-Synthese DL-Serin mit 70% Ausbeute. Diese Methode ergab, direkt von den „maskierten" Glycolaldehyden **2**, **7**, **9**, **10**, Vinylencarbonat (**11**), **13** oder **14** ausgehend, ebenfalls DL-Serin (Ausbeuten 35–70%), wogegen ausgehend von **4** kein Serin nachgewiesen werden konnte.

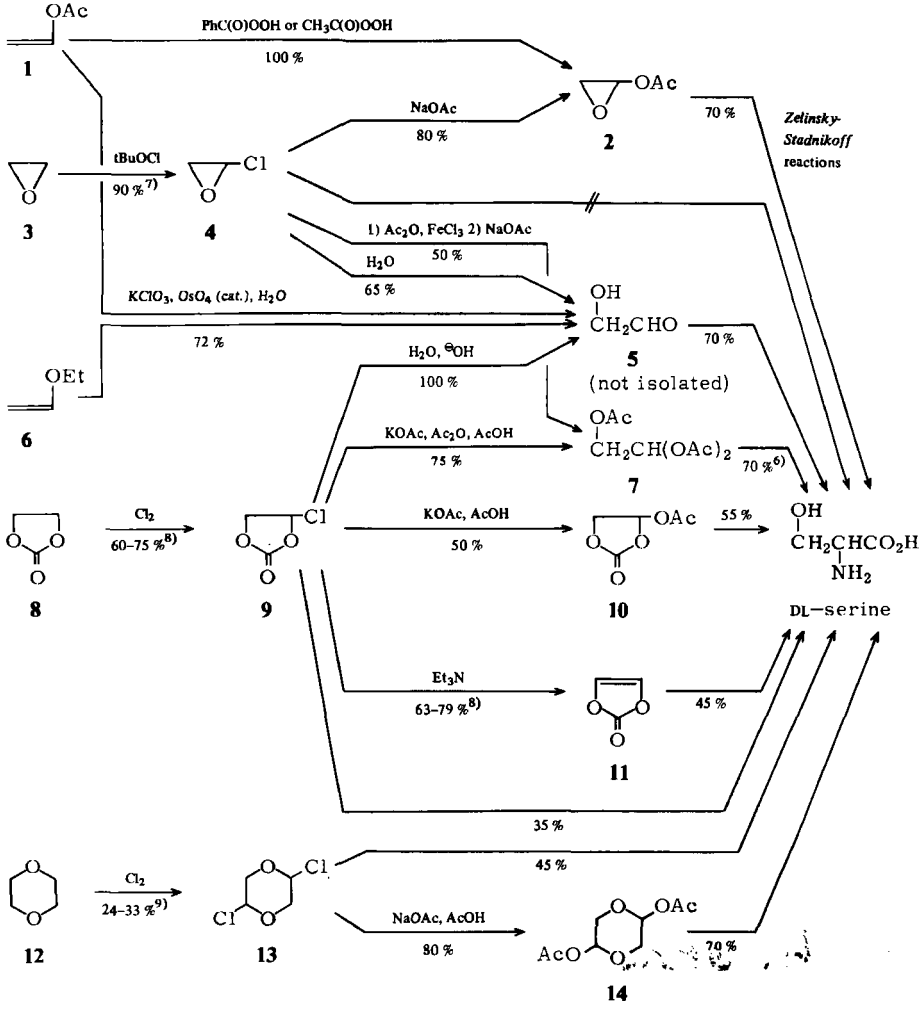
The present paper reports the principal results of a research aimed at finding commercial syntheses of DL-serine from inexpensive starting materials. Our interest on this topic relied on the possibility of developing an industrial process of L-tryptophan preparation from indole and DL-serine using fibre-entrapped tryptophan synthetase[1].

It is known that DL-serine can be obtained from glycolaldehyde (**5**) in a yield of 54% by a modified *Bucherer-Bergs (B.-B.)* reaction[2] and of 9% by the *Strecker* method[3]. However, in preliminary experiments we found that the *Zelinsky-Stadnikoff (Z.-S.)* modification of the *Strecker* synthesis allows to prepare serine from **5** in a quite superior yield (70%). It is further known that also 1,1,2-triacetoxyethane[4] (**7**), a "masked" glycolaldehyde which liberates **5** in alkaline medium, affords serine in 70% yields either by the classical *B.-B.*[5] or by the *Z.-S.*[6] procedure. In view of these facts, our research program was developed according to the following lines. (a) Search for inexpensive syntheses of **5** by development of the known ones which appeared to be economically more promising, or by new methods. (b) Search for alternative, economical, syntheses of **7**, the known one[4] requiring the use of the costly bromine. (c) Search for "masked" alkali-labile glycolaldehydes, other than **7**, as potential inexpensive precursors of serine. As

candidates for the latter class were chosen vinyl acetate epoxide (**2**), vinyl chloride epoxide (**4**), chloroethylene carbonate (**9**), acetoxyethylene carbonate (**10**), vinylene carbonate (**11**) and, finally, the two "masked" dimeric glycolaldehydes 2,5-dichlorodioxane (**13**) and 2,5-diacetoxydioxane (**14**). Except **10**, all these potential precursors of serine were already known compounds. Moreover it was seen that the published syntheses of these latter compounds utilize inexpensive precursors but that, in the case of **2**, **13**, and **14**, the reported yields are low and that costly reagents were used for the synthesis of **2** and **14**. The known syntheses of these three derivatives required, therefore, an improvement.

A synopsis of the principal results of the present investigation and of the complementary ones from literature is given in scheme 1.

scheme 1



Syntheses

Vinyl acetate epoxide (oxiran-2-yl acetate) (2)

a) *From vinyl acetate* (**1**): The epoxidation of **1** with perbenzoic acid in chloroform at 5°C has been reported previously, but **2** was obtained in low isolated yield (25%)[10]. The use, however, of excess perbenzoic acid and of a less destructive work-up procedure (see experimental part) allowed us to improve considerably the isolated yields of **2** (83 to 93%).

Our interest for the epoxidation of **1** relied primarily on the possibility of using, as epoxidizing agent, the cheaper peracetic acid. Due to a relative general instability of **2**, it was found preferable to use peracetic acid solutions that were free of undesirable substances like water, hydrogen peroxide, strong acids, alcohols, etc. From the known methods[11,12] for the preparation of peracetic acid the most convenient for our purpose turned out to be the one of *Ogata* and *Sawaki*[12] based on alkaline perhydrolysis of acetic anhydride with 30% hydrogen peroxide/sodium hydroxide.

In a preliminary experiment of epoxidation of **1** (0°C) with the 40% peracetic acid solution obtained, a stoichiometric amount of peracid was used. However, the course of the reaction indicated that, under these conditions, most of the formed **2** evolves further with additional and competitive (with respect to **1**) consumption of peracid[13]. A plausible explanation of this phenomenon can be found in an acetic acid-catalyzed rearrangement of **2** to acetoxyacetaldehyde[14], followed by a *Baeyer-Villiger* type oxidation of the aldehyde by peracetic acid[15].

On carrying out the epoxidation with a 8:1 volumetric ratio between **1** and the peracetic acid solution (in the stoichiometric experiment this ratio was 0.5:1), GC analysis of the reaction mixture revealed quantitative formation of **2** (based on peracid). The yield of isolated **2**, free of acetoxyacetaldehyde (^{1}H NMR: absence of aldehydic protons), was 65%. In analogy to the case of the epoxidation with perbenzoic acid (see above), the lower value found for the isolated yield was due only to the fact that part of **2** distilled together with the lower-boiling components (essentially excess **1**) when these were removed.

An alternative methodology aimed at preventing the acid-catalyzed rearrangement of **2** during epoxidation of **1** with the 40% peracetic acid, i.e., epoxidation in the presence of sodium hydrogen carbonate or dibasic sodium phosphate (in order to neutralize the acetic acid)[16], was unsuccessful.

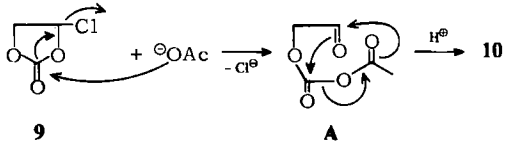
b) *From vinyl chloride epoxide (2-chlorooxirane)* (**4**): Acetoxylation of **4** could be performed directly with the reaction mixture ensuing from the chlorination of excess ethylene oxide (**3**) with *tert*-butyl hypochlorite (carried out essentially according to *Walling* and *Fredricks*[7a], as described under Materials), **3** being inert to the acetoxylation conditions. Finally, it was found that for the preparation of serine it is advantageous to use directly the filtered acetoxylation mixture from which only the excess **3** was removed. In fact, isolation of **2** from this solution caused a 15% loss of product (yield of isolated **2**, 66%) and the *Z.-S.* reaction could be carried out on said solution with the same yield as when starting from the isolated **2**.

Acetoxyethylene carbonate (10)

Of the various metal acetates and solvents tested for the acetoxylation of **9**, silver acetate in toluene (24 h reflux) and potassium acetate in acetic acid (15 h reflux) afforded

the highest unisolated yields of **10** (85% by GC analysis of either reaction mixture). Isolation of the product from the latter acetoxylation mixture by a procedure involving distillation of **10** gave rise, however, to substantial losses of product by decomposition (yield of isolated **10**, 50%).

With regard to the mechanism of formation of **10** from **9**, while for the silver acetate/toluene system a direct substitution of chlorine by acetate can be postulated (Ag^+ ions are well-known to markedly accelerate nucleophilic substitution reactions of alkyl halides), for the potassium acetate/acetic acid system, a different type of mechanism seems to prevail. This assumption is based on the outcome of one of the preliminary acetoxylation experiments in which **9** was treated with sodium acetate in toluene (30 h reflux). Gas chromatography/mass spectrometry analysis of this reaction mixture revealed that the solution contained – in addition to substantial amounts of unreacted **9** and to only traces of **10** – a sizable quantity of a product with same molecular weight as **10** but with a different fragmentation pattern: m/e = 145 ($M^+ - H$), 131, 117, 103, 29 (for **10**: see exp. part). This pattern is in accordance with structure **A**, and the formation of this product from **9** can be easily explained taking into account the following mechanism [17].

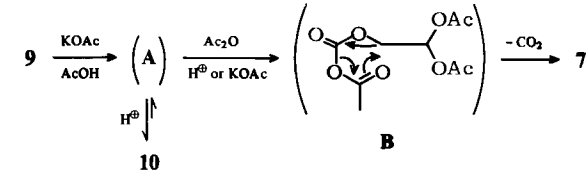


(1)

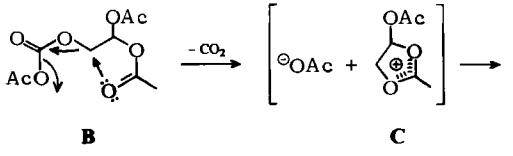
This finding, and the related reactions in protic solvents [17], suggest that formation of **A** occurs also in the acetoxylation of **9** with potassium acetate in acetic acid (more efficiently than with the sodium acetate/toluene system, due to the higher solubility of potassium acetate in acetic acid), but that in the latter case **A** undergoes, *in situ*, acetic acid-catalyzed rearrangement to **10** [18].

1,1,2-Triacetoxyethane (7)

a) *From chloroethylene carbonate* (**9**): The above postulated formation **A** in the acetoxylation of **9** with sodium acetate in toluene or, in higher yield, with potassium acetate in acetic acid, led us to hypothesize a new, one-step synthesis of **7** from **9**. We thought, in fact, that addition of acetic anhydride to the latter acetoxylating system might allow to divert the intermediate **A** [19] toward formation of **7** *via* **B** [20, 21] as given in (2). For **B** → **7** a decarboxylation mechanism assisted anchimerically by the geminal acetoxy groups was also postulated (3).



(2)

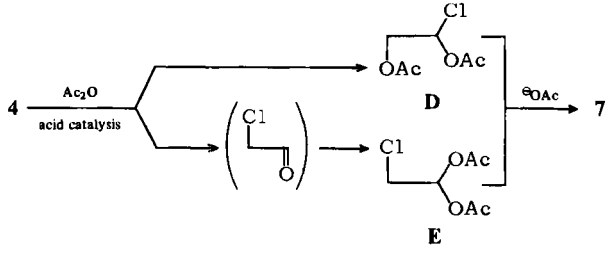


(3)

Preliminary experiments demonstrated, indeed, that this synthesis was realizable. In fact, after treatment of **9** with equimolar acetic anhydride and a slight excess of potassium acetate in acetic acid (about 30 h reflux), GC analysis revealed formation of **7** in about 40% yield and of **10** in only minor amounts (other, unidentified products being also formed). Furthermore, when the reaction was applied to **10** – using only a catalytic amount of potassium acetate – the outcome of the GC analysis was, after 80 h reflux, practically the same as above. With substrate **9** and a higher potassium acetate excess even 75% **7** were isolated. In this experiment, GC revealed concomitant formation of **10** and **7** at the earlier stages of the reaction, and increase of the latter product at the expense of the former as the reaction proceeded.

The higher yield of **7** obtained using a greater potassium acetate concentration may be explained on the basis of one, or both, of the following hypotheses: (1) the transformation **B** → **7** occurs by a bimolecular substitution process involving intermolecular attack of acetate ion on **B**; (2) the transformation **A** → **B** is catalyzed by acetate and requires a relatively high acetate concentration as in the case of other aldehydes[22].

b) *From vinyl chloride epoxide* (**4**): The possibility of preparing **7** also from **4**, by acid-catalyzed reaction with acetic anhydride – to give **D** and/or **E**[23] – followed by treatment with an acetate salt, was also investigated.



(4)

This synthesis was realized by treatment of **4** with acetic anhydride and a catalytic amount of ferric chloride followed by sodium acetate. This one-pot procedure afforded **7** in a 50% isolated yield. GC revealed formation of two major products with almost equal retention times during acetic anhydride treatment, and conversion of both products to **7** by sodium acetate at different rates. The behaviour of these two intermediates is as would be expected for derivatives **D** and **E**; investigations aimed at confirming these structures were, however, not undertaken.

2,5-Diacetoxydioxane (14)

Previously, **14** was prepared either by acetoxylation of **13**[9a], or of the corresponding dibromo derivative[24], with silver acetate in toluene, or by acetylation of dioxane-2,5-diol (dimer of **5**) with acetic anhydride and pyridine[25]. In the first two cases a crystalline product identified later[26] by ^{1}H NMR analysis as the *trans*-isomer with diaxial chair conformation was isolated in unspecified yields (on repeating the literature[9a] procedure, we found the yield of this product to be 21% from **13**). In the third case there was isolated, in addition to the above crystalline diacetate (yield, 50%), an oily stereoisomer (yield, 20%), whose stereochemistry, to our knowledge, has never been reported previously in the literature.

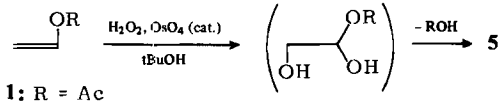
With the purpose of economically improving the preparation of **14** from **13**, we investigated the acetoxylation of the latter with sodium or potassium acetate under various conditions. The best yield was obtained with sodium acetate in acetic acid at room temperature: 80% of **14** as a semisolid with single GC peak. On crystallization of this product from ethanol, a derivative was isolated (yield, 33%) that was identical with the above-mentioned *trans*-isomer. Removal of the solvent from the crystallization mother liquor and vacuum distillation of the residue afforded an oily product. The ^1H NMR spectrum (C_6D_6) of the latter was in line with structure **14** and showed, in addition to a singlet at $\delta = 1.65$ for the acetoxylic protons, an approximate quartet at $\delta = 5.15$ for 2- and 5-H and two quartets, at $\delta = 3.75$ and 3.40, for the methylene C-3 and C-6 protons with coupling constants $J'_{vic} = +5.2$, $J''_{vic} = +3.4$ and $J_{gem} = -12.0$ Hz. The values found for the *vicinal* couplings are in accord (for a discussion see [26]) with a *cis* configuration and an axial-equatorial chair conformation for the oily isomer.

Glycolaldehyde (5)

a) *From chloroethylene carbonate* (**9**): It is known[27] that **5** can be prepared by hydrolysis of **9** with various bases. However, of the reported yields of **5** (isolated by distillation), the only satisfactory one (72%) is that claimed for the hydrolysis with the costly and highly toxic lead monoxide, while with potassium hydrogen carbonate or sodium hydroxide the yields are reported to be about 40%. Moreover, on repeating the literature[27] procedure for the hydrolysis of **9** with lead monoxide and for the isolation of **5**, we were unable to reach the claimed yield. In fact, during the vacuum distillation of **5**, extensive polymerization of the product occurred, and the yield of isolated **5** did not exceed 25%, even when the distillation was carried out under milder conditions as the ones reported. On the other hand, titrimetric dosage (hydroxylamine hydrochloride method[28])[29] of the reaction mixture after filtration from the lead salts, neutralization and GC control for absence of **9**, indicated that in this experiment the formation of **5** was quantitative. Furthermore, when the *Z.-S.* reaction was performed directly on the above, filtered reaction mixture, serine could be obtained in a 70% overall yield from **9**, as when starting from the isolated **5** (which confirms the quantitative formation of **5** in the hydrolysis of **9** with lead monoxide). For these reasons, in the hydrolysis studies with bases other than lead monoxide, the isolation of **5** was omitted. These experiments demonstrated that also with sodium hydrogen carbonate, sodium carbonate, sodium hydroxide, or potassium hydrogen carbonate a quantitative formation of **5**, and a 70% yield of serine after *Z.-S.* reaction, can be achieved, provided that the hydrolysis of **9** is carried out under accurate temperature and pH control (to prevent polymerization of **5**).

b) *From vinyl chloride epoxide* (**4**): Also the hydrolysis of **4**, not described previously in the literature, represented an economical route to **5**. On treatment of **4** with water, either at constant pH 7 or 4 (automatic titrator charged with diluted sodium hydroxide), or in the presence of a stoichiometric amount of suspended calcium carbonate, the conversion of **4** was complete (GC), but the yield of unisolated **5** unsatisfactory. In fact, the subsequent *Z.-S.* reaction on these solutions afforded serine in about 20% overall yield from **4**, which corresponds to a yield for **5** of about 30%[29,30]. Finally, treatment of **4** with water under "free" pH permitted to obtain, after the *Z.-S.* reaction, a higher overall yield of serine: 45% corresponding to a 65% yield for **5**.

c) *From vinyl acetate* (**1**) *or ethyl vinyl ether* (**6**): Another known method for the synthesis of **5** is the one of *Milas* et al.[31] based on the oxidation of **1**, or divinyl ether (**15**), with an anhydrous solution of hydrogen peroxide and catalytic osmium tetroxide in *tert*-butyl alcohol (5). The yields, based on converted substrate, are reported to be 60% from **1** and 96% from **15**, but the per cent conversion of the two olefins is not specified. Moreover, while in the first case the yield refers to **5** isolated by distillation, in the second case the aldehyde **5** was estimated by precipitation of its *p*-nitrophenylosazone from the crude reaction product.



(5)

1: R = Ac

15: R = $CH{=}CH_2$

It is further known[32] that olefins other than enol derivatives have been oxidized – in the presence of catalytic osmium tetroxide – also with a metal chlorate in aqueous solution, affording α-diols generally in high yields. Being this procedure cheaper and operatively simpler than the one making use of an anhydrous hydrogen peroxide solution, we investigated its applicability also to vinyl esters or vinyl ether like **1** or **6**.

When **1**, or **6**, was oxidized with aqueous potassium chlorate and catalytic osmium tetroxide, and the reaction mixture, after selective removal of the osmium tetroxide with benzene, was submitted to the *Z.-S.* reaction, serine was obtained in an overall yield from **1** or **6** of 50%, a value corresponding to a 72% yield for **5**.

Synthesis of DL-Serine

For the study of the synthesis of serine from **5** and from the "masked" glycolaldehydes **2**, **4**, **9**–**11**, **13** and **14** the *Z.-S.* procedure used by *Geipel* et al.[6] for substrate **7** was utilized. Except **4**, all these substrates afforded serine, the yields being 70% from **2**, **5** or **14** (both stereoisomers), 35% from **9**, 55% from **10**, 45% from **11** or **13**.

With substrates **5** and **10**, also the *B.-B.* reaction was tried (utilizing the procedure described[5] for **7**), but the yields of serine fell quite lower (30 and 10%, respectively) than with the *Z.-S.* reaction.

We wish to express our thanks to Dr. *L. Settembri* for the ^{1}H NMR spectra and to Dr. *A. Robertiello* for the mass spectra.

Experimental Part

Materials: Vinyl acetate (**1**), ethylene carbonate (**8**) and osmium tetroxide were obtained from Merck AG (Darmstadt, Germany). Ethylene oxide (**3**) and ethyl vinyl ether (**6**) were from Fluka A.G. (Buchs, Switzerland). Perbenzoic acid was prepared according to *Braun*[33]. A 40% peracetic acid solution in acetic acid (50%) and methylene chloride (10%) was prepared – in an adaptation of the *Ogata* and *Sawaki*[12] method – by alkaline perhydrolysis (2 h at room temperature) of acetic anhydride (23.5 ml) with 30% hydrogen peroxide (75 ml) and sodium hydroxide (30 g) in water (300 ml) in the presence of magnesium sulfate heptahydrate (1.25 g), followed by acidification with 20% sulfuric acid (150 ml), repeated extraction with methylene chloride (total volume, 1.5 l) and final removal of the solvent from the organic phase by distillation at atmospheric pressure through a 1 m Vigreux column: peracid yield, 15% by titration. *tert*-Butyl hypochlorite was

prepared according to *Teeter* and *Bell*[34]. Vinyl chloride epoxide (**4**) solutions in ethylene oxide (**3**) and *tert*-butyl alcohol were prepared – essentially according to *Walling* and *Fredricks*[7a] – by irradiation (100 Watt incandescent lamp; 2 h at 0°C and under N_2) of a 6 : 1 molar mixture of **3** and *tert*-butyl hypochlorite; dosage of the formed **4** was carried out by treatment of 1 ml of the reaction mixture with 10 ml of 1 N NaOH followed by back-titration of the excess base: titrated yield, 88% (based on hypochlorite). Chloroethylene carbonate (**9**), vinylene carbonate (**11**) and 2,5-dichlorodioxane (**13**) were prepared according to literature[8,9]. All other materials (RPE-ACS grade) were from Carlo Erba (Milano, Italy).

General: ^{1}H NMR spectra: Varian T-60 spectrometer, tetramethylsilane as internal standard. – Mass spectra: Varian MAT 111 instrument (ionizing energy, 70 eV). – IR spectra: Perkin-Elmer 457 spectrometer. – GC analyses were performed as follows: (1) With a Hewlett-Packard 7620-A gas chromatograph equipped with a thermal conductivity detector using the following columns: (A) 6 ft × 1/8 in. 10% OV-17 on silanized Chromosorb W (80–100 mesh); (B) 10 ft × 1/8 in. 5% Carbowax 20 M on silanized Chromosorb W (60–80 mesh); (C) 6 ft × 1/8 in. 10% Carbowax 20 M on silanized Chromosorb G (60–80 mesh). (2) With a Carlo Erba Fractovap C type ATC/F gas chromatograph equipped with a thermal conductivity detector using the following column (D): 5 m × 6 mm 10% E 301 on silanized Chromosorb W (80–100 mesh). – TLC of serine was carried out on silica gel 60 F_{254} plates (Merck AG) of 0.25 mm layer thickness eluting with n-butanol/acetic acid/water (60 : 20 : 20, by vol.), R_F 0.19.

Vinyl acetate epoxide (oxiran-2-yl acetate) (**2**)

a) *From vinyl acetate* (**1**) *with perbenzoic acid:* A solution of 2.76 g (32.06 mmol) of **1** and 6.70 g (48.51 mmol) of perbenzoic acid in 100 ml of chloroform was allowed to stand at 0°C for 7 days. Then GC analysis [column A at 50°C for 5 min, then 50 → 130°C (30°C/min) and with 15 ml/min of He, using n-undecane as internal standard] of the solution revealed quantitative formation of **2**. The epoxide was stripped together with the solvent at 0.1 Torr (10°C bath temp.), collecting the distillate in a liquid air cooled trap. The distillate was redistilled at 40 Torr (20°C bath temp.) through a Liebig fractionating column (10 × 0.8 cm) charged with Raschig rings and cooled externally to 6°C (to assure partial reflux), collecting the distillate in a liquid air cooled trap. Finally, a residue was obtained, 3.76 g of **2** of 81% purity (by GC, the balance to 100% being residual chloroform), corresponding to a 93% yield corrected for pure **2**; the destillate consisted of the bulk of the solvent containing the rest of **2** (7%). In order to remove further the solvent from the crude **2**, the latter was concentrated, without the Liebig column, at 20 Torr (20°C bath temp.) until the residue consisted (GC) of 96% pure **2** (4% chloroform): there was obtained 2.83 g of product, corresponding to an 83% yield corrected for pure **2**.

IR: identical with the one reported in literature[10]. – ^{1}H NMR (C_6D_6): δ = 1.70 (s; 3 H, CH_3), 2.25 and 2.60 (dq, J_{gem} = 4.6, J_{vic} = 2.4 and 1.3 Hz; 2 H, CH_2), 5.43 (q, J = 2.4 and 1.3 Hz; 1 H, CH). – MS: *m/e* = 103, 74, 73, 43, 42, 15.

b) *From* **1** *with peracetic acid:* To 52.00 g (0.604 mol) of **1** was added a trace of radical inhibitor 2,6-di-*tert*-butyl-*p*-cresol and 7.0 ml of a 40% peracetic acid solution (see under Materials) (corresponding to 0.037 mol of peracid). After 7 days at 0°C, GC analysis (conditions as above) revealed quantitative formation of **2** (based on peracid). To the solution was added 9.25 g (0.11 mol) of sodium hydrogen carbonate and the suspension stirred for 3 h at room temp. to neutralize the acetic acid. The suspension was filtered and the precipitate washed with a little methylene chloride. The removal of the lower-boiling components from the combined filtrates was performed essentially as for the case of the chloroform solution of **2** obtained under a), the only differences being as follows. (1) The distillation through the Liebig column was carried out at 20 Torr (15°C bath temp.) with a cooling of the column at 10°C and gave, as residue, 3.93 g of **2** of 81% purity (by GC, the balance to 100% being a 3 : 1 mixture of **1** and acetic acid), correspond-

ing to a 84% yield corrected for pure **2** (yield based on peracid); the distillate consisted of the excess **1** containing the methylene chloride, the rest of **2** (16%) and traces of acetic acid. (2) The crude **2** was concentrated at 50 Torr (20 °C bath temp.) to a 2.58 g residue of **2** of 95% purity (by GC, the balance to 100% being acetic acid and traces of **1**), corresponding to a 65% yield corrected for pure **2** (yield based on peracid). – ^{1}H NMR and IR spectra: identical with those in a).

c) *From vinyl chloride epoxide* (**4**): A 10 ml solution of 1.55 g (19.74 mmol) of **4** in *tert*-butyl alcohol and **3** (see Materials) was added dropwise over a 5 min period, under ice-bath cooling and N_2 atmosphere, to a stirred suspension of 1.95 g (23.77 mmol) of anhydrous sodium acetate in 15 ml of anhydrous ethanol. After 20 h stirring under the same conditions, the suspension was filtered at 5 °C and the precipitate washed with a little methylene chloride. From the combined filtrates **3** was removed selectively at about 300 Torr (0 °C bath temp.). GC analysis (conditions as above) of the residue revealed formation of **2** in 80% yield [for the preparation of serine it is preferable (see General Section) to carry out the *Z.-S.* reaction directly on this residue]. Removal of the lower-boiling components from the residue as described for the isolation of the 96% pure **2** in a) gave 1.47 g of **2** of 90% purity (by GC, the balance to 100% being an unidentified by-product, with higher retention time as for **2**, and a little *tert*-butyl alcohol), corresponding to a 66% yield corrected for pure **2**. – ^{1}H NMR and IR spectra: identical with those in a).

Acetoxyethylene carbonate (4-acetoxy-1,3-dioxolan-2-one) (**10**): A mixture of 9.19 g (75.01 mmol) of **9** and 7.36 g (74.99 mmol) of potassium acetate in 100 ml of glacial acetic acid was refluxed for 15 h under stirring and N_2 atmosphere. The mixture was filtered at room temp. from the salts and the precipitate washed with ether. GC analysis [column B at 175 °C for 6 min, then 175 → 190 °C (20 °C/min), finally at 190 °C for 5 min and with 20 ml/min of He, using **8** as internal standard] of the combined filtrates revealed formation of **10** in 85% yield. The solution was then concentrated on a rotary evaporator to about 50 ml and, after addition of about 100 ml of ether, the precipitated salts were filtered. After washing of the precipitate with ether, the combined filtrates were reconcentrated on a rotary evaporator to an oily residue. Distillation of the latter afforded 5.50 g (50%) of GC pure **10** as a thick oil, b.p. 132–134 °C/3 Torr.

IR (film): 1820 (carbonate C=O), 1758 (acetate C=O); 1230 (acetate C–O), 1160, 1090 and 995 cm^{-1} (carbonate C–O)[35]. – ^{1}H NMR (C_6D_6): δ = 1.65 (s; 3 H, CH_3), 3.85 (d; J = 4.5 Hz; 2 H, CH_2), 6.50 (t; J = 4.5 Hz; 1 H, CH). – MS: m/e = 146, 103, 87, 43.

$C_6H_6O_5$ (146.1) Calcd. C 41.10 H 4.14 Found C 41.13 H 4.15

1,1,2-Triacetoxyethane (**7**)

a) *From chloroethylene carbonate* (**9**): A mixture of 3.30 g (26.94 mmol) of **9**, 0.55 g (56.04 mmol) of potassium acetate and 2.65 ml (27.81 mmol) of acetic anhydride in 30 ml of glacial acetic acid was refluxed for 40 h under stirring and N_2 atmosphere. After cooling to room temp., 70 ml of methylene chloride was added and the precipitated salts removed by filtration. GC analysis (column D at 165 °C, 30 ml/min of He, using styrene as internal standard) of the filtrate revealed formation of 7 in 85% yield. The solution was evaporated to dryness on a rotary evaporator and the residue treated with charcoal in methylene chloride. After filtration, the solution was re-evaporated to dryness on a rotary evaporator and the residue, 5.08 g of **7** of 90% purity (by GC, corresponding to an 83% yield corrected for pure **7**), purified by distillation to give 4.13 g (75%) of GC pure **7**, b.p. 112–114 °C/2 Torr (lit.[36] 115–130 °C/5 Torr), m.p. 48–50 °C (lit. 44–46 °C[4], 51–52 °C[36]). – IR (nujol): 1760 (C=O), 1200, 1142, 1110, 1050 and 1010 cm^{-1} (C–O). – ^{1}H NMR (C_6D_6): δ = 2.11 (s; 9 H, CH_3), 4.28 (d; J = 4.5 Hz; 2 H, CH_2), 6.98 (t; J = 4.5 Hz; 1 H, CH). These spectra were identical with those of a sample of **7** prepared according to literature[4].

b) *From vinyl chloride epoxide* (**4**): To 16 ml of a solution of 5.27 g (67.13 mmol) of **4** in *tert*-butyl alcohol [prepared according to Materials followed by stripping, at 0 °C, of the excess **3**

with a N_2 stream (the stripping caused also partial removal of **4**)] was added 40 ml of acetic anhydride and 0.22 g of ferric chloride and the mixture stirred for 1 h at room temp. under N_2 atmosphere. After addition of 5.51 g (67.16 mmol) of anhydrous sodium acetate, the mixture was stirred, still under N_2, at room temp. for 60 h and then at reflux for 48 h. After cooling to room temp., the mixture was diluted with 100 ml of methylene chloride and worked up as in a). The distillation at 2 Torr gave 6.86 g (50%) of GC pure **7**, identical in all respects to the product obtained from **9**.

2,5-Diacetoxydioxane (**14**): A solution of 1.87 g (11.91 mmol) of **13** in 6 ml of glacial acetic acid was added dropwise over a 5 min period, at room temp. and under N_2 atmosphere, to a stirred suspension of 2.44 g (29.74 mmol) of anhydrous sodium acetate in 20 ml of glacial acetic acid. After 2 h stirring under the same conditions, the acetic acid was removed under 3 Torr at room temp. The residue was stirred for 2 h at room temp. with 450 ml of ethyl acetate, in order to extract selectively **14** from the salts and from other organic products[37]. After filtration and rotary evaporation of the solvent (bath temp. ≤ 40°C), there was obtained 1.94 g (80%) of **14** as a semisolid with single GC peak (column C at 190°C, 20 ml/min of He). Crystallization from ethanol gave 0.80 g (33%) of the *trans*-**14** isomer with diaxial chair conformation, m.p. 156–157°C (Lit.[24] 157–158°C). – ^{1}H NMR (C_6D_6): identical with that reported in literature[26]. When the crystallization mother liquors obtained from a few acetoxylation runs were combined and the ethanol removed (rotary evaporator), the *cis*-**14** isomer with axial-equatorial chair conformation could be isolated by distillation of the residue, b.p. 100°C/1 Torr. – ^{1}H NMR: in accord with the proposed structure (see general section).

DL-Serine

a) *From glycolaldehyde* (**5**), *vinyl acetate epoxide* (**2**), *chloroethylene carbonate* (**9**), *acetoxyethylene carbonate* (**10**), *vinylene carbonate* (**11**), *2,5-dichlorodioxane* (**13**), *and 2,5-diacetoxydioxane* (**14**). *General procedure:* A solution of 20.00 mmol of substrate (10.00 mmol for **13** and **14**) in 15 ml of methanol was added under cooling (reaction temp. ≤ 30°C) to a stirred solution of 1.30 g (19.97 mmol) of potassium cyanide and 1.18 g (22.06 mmol) of ammonium chloride in 10 ml of about 30% ammonia in water. The mixture was stirred at 30–35°C for 18–20 h, then acidified with 11 ml of conc. hydrochloric acid and evaporated to dryness on a rotary evaporator (60°C). The residue was refluxed for 4–5 h in 11 ml of conc. hydrochloric acid and 11 ml of water, then re-evaporated to dryness on a rotary evaporator. The residue was taken up in 10 ml of anhydrous ethanol removing the undissolved salts by filtration and the filtrate adjusted to pH 6.0 with triethylamine. After cooling, the precipitated serine was collected by filtration and, when necessary, purified by charcoal treatment in water and/or by recrystallization from water/ethanol. The yields of serine, identical (m.p., IR and TLC) with an authentic sample (Fluka AG), were as follows: 70% from **2**, **5** or **14** (both stereoisomers); 35% from **9**; 55% from **10**; 45% from **11** or **13**.

b) *From* **9** *via* **5**: To 2.45 g (20.00 mmol) of **9** was added dropwise, under cooling and vigorous stirring, a solution of 1 equiv. of base (sodium hydrogen carbonate, sodium carbonate, sodium hydroxide, or potassium hydrogen carbonate) in 6 ml of water (for sodium hydrogen carbonate the part of base not soluble in 6 ml of water was added, subsequently, in the solid state), regulating the addition rate in such a way as to keep the pH of the reaction mixture at alkaline values (not over pH 8–9) for the shortest time possible and the temperature at not more than 25°C (5°C in the case of sodium hydroxide). After the addition was completed (30–60 min), the mixture was stirred at room temp. until the **9** layer had disappeared, carbon dioxide generation had ceased, and GC control (column B at 205°C, 20 ml/min of He) of the solution had confirmed the absence of **9** (2–3 h). Titrimetric dosage of the neutralized solution by the hydroxylamine hydrochloride method[28] indicated a quantitative formation of **5**. To the stirred aqueous solution of **5** was added under cooling (reaction temp. ≤ 30°C) a solution of 1.30 g (19.97 mmol) of potassium cyanide and

1.18 g (22.06 mmol) of ammonium chloride in 10 ml of about 30% ammonia in water and 10 ml of methanol. Proceeding as described above (General Procedure), 1.47 g (70% from **9**) of TLC pure serine was obtained.

c) *From vinyl chloride epoxide* (**4**) *via* **5**: To 10 ml of water was added dropwise, under stirring and cooling (reaction temp. $\leq 5°C$), 5 ml of a solution of 1.57 g (20.00 mmol) of **4** in *tert*-butyl alcohol (prepared as described under the preparation of **7** from **4**). After 2 h stirring at room temp., GC analysis (column A at 50°C, 15 ml/min of He) of the solution showed desappearance of **4**. To the stirred solution was added under cooling (reaction temp. $\leq 30°C$) a solution of 1.30 g (19.97 mmol) of potassium cyanide in 15 ml of about 30% ammonia in water[38]. Proceeding as described obove (General Procedure), 0.95 g (45% from **4**) of TLC pure serine was obtained.

d) *From vinyl acetate* (**1**) *via* **5**: A mixture of 1.72 g (19.98 mmol) of **1**, 10 ml of water, 2.80 g (22.85 mmol) of potassium chlorate and 0.10 g (0.39 mmol) of osmium tetroxide was stirred at room temp. for 20 min; at the end of this period the mixture, originally dark, had become light pink. The osmium tetroxide was removed selectively by repeated extractions with benzene, and to the aqueous phase was added under cooling (reaction temp. $\leq 30°C$) a solution of 1.30 g (19.97 mmol) of potassium cyanide and 1.18 g (22.06 mmol) of ammonium chloride in 10 ml of about 30% ammonia in water. Proceeding as described above (General Procedure), 1.05 g (50% from **1**) of TLC pure serine was obtained.

e) *From ethyl vinyl ether* (**6**) *via* **5**: A mixture of 1.44 g (19.97 mmol) of **6**, 10 ml of water, 2.80 g (22.85 mmol) of potassium chlorate and 0.10 g (0.39 mmol) of osmium tetroxide was stirred at room temp. for 4 h maintaining the pH of the mixture at 6.8 – 7.0 with an automatic titrator charged with 1 N NaOH. After removal of the osmium tetroxide by repeated extractions with benzene, a titrimetric dosage of the aqueous phase by the hydroxylamine hydrochloride method[28] indicated formation of **5** in 72% yield. Treatment of the aqueous phase as in d) afforded 1.04 g (50% from **6**) of TLC pure serine.

Literature

[1] *P. Zaffaroni, V. Vitobello, F. Cecere, E. Giacomozzi,* and *F. Morisi,* Agr. Biol. Chem. **38**, 1335 (1974).

[2] *Röhm & Haas G.m.b.H.*, Neth. Appl. 6607754 (Dec. 5, 1966) [Chem. Abstr. **67**, P 73159b (1967)].

[3] *E. Fischer* and *H. Leuchs*, Ber. Dtsch. Chem. Ges. **35**, 3787 (1902).

[4] *H. Gross, K.-P. Hilgetag, J. Gloede,* and *H. Geipel*, Chem. Ber. **98**, 1673 (1965).

[5] *J. Budnik, J. Lukac,* and *M. Borovicka*, Czech. Pat. 126464 (March 15, 1968) [Chem. Abstr. **70**, P 29297h (1969)].

[6] *H. Geipel, J. Gloede, K.-P. Hilgetag,* and *H. Gross*, Chem. Ber. **98**, 1677 (1965). These authors report an 87.5% yield of serine from **7**; on repeating, however, the author's procedure we found the above value to correspond to a crude yield, the yield for the recrystallized, TLC pure, serine being 70%.

[7] [7a] *C. Walling* and *P. S. Fredricks*, J. Am. Chem. Soc. **84**, 3326 (1962). – [7b] *C. Walling* and *M. J. Mintz*, ibid. **89**, 1515 (1967).

[8] *W. R. Sorenson* and *T. W. Campbell*, Preparative Methods of Polymer Chemistry, 2nd ed, pp. 261 – 262, Wiley, New York, N. Y. 1968, and refs. cited therein. It is to be noted that we could obtain a 75% yield of **9** also by using for the irradiation, in place of the UV lamp, an incandescent one (250 Watt).

[9] [9a] *L. A. Bryan, W. M. Smedley,* and *R. K. Summerbell*, J. Am. Chem. Soc. **72**, 2206 (1950). – [9b] *W. M. Smedley*, US-Pat. 2414982 (Jan. 28, 1947) [Chem. Abstr. **41**, P 2755g (1947)].

[10] *B. S. Gorton* and *J. A. Reeder*, J. Org. Chem. **27**, 2920 (1962).

[11] [11a] *B. Phillips, F. C. Frostick,* and *P. S. Starcher*, J. Am. Chem. Soc. **79**, 5982 (1957). – [11b] *E. I. du Pont de Nemours and Co.* (Inv. *J. G. Wallace*), US-Pat. 2833813 (May 6, 1958) [Chem. Abstr. **52**, P 14658c (1958)]. – [11c] *E. I. du Pont de Nemours and Co.* (Inv. *D. R. V.*

Golding), US-Pat. 2833814 (May 6, 1958) [Chem. Abstr. **52**, P 14658d (1958)]. – [11d] *J. G. Wallace* in Encyclopedia of Chemical Technology (*R. E. Kirk* and *D. F. Othmer*), Vol. 8, pp. 238–263, Wiley, New York, N.Y. 1965.

[12] *Y. Ogata* and *Y. Sawaki*, Tetrahedron **23**, 3327 (1967).

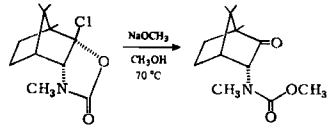
[13] A blank assay on the stability of the peracetic acid solution (6 days at 0°C) permitted to exclude that the observed peracid consumption was due to spontaneous decomposition.

[14] Acid-catalyzed rearrangements of enol acetate epoxides to α-acetoxy ketones are well-known, see *H. O. House*, Modern Synthetic Reactions, 2nd ed, pp. 315–316, W. A. Benjamin, Menlo Park, Calif. 1972.

[15] For *Baeyer-Villiger* type oxidations of aldehydes to carboxylic acids and/or formic acid esters see *C. H. Hassal*, Org. React. **9**, 73 (1957); *C. R. Zanesco*, Helv. Chim. Acta **49**, 1002 (1966); cf. also [11a].

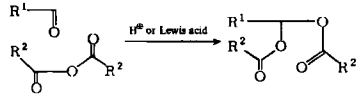
[16] For epoxidations with peracids in the presence of a base see *H. O. House*[14], pp. 299–300; *M. Korach, D. R. Nielsen*, and *W. H. Rideout*, J. Am. Chem. Soc. **84**, 4328 (1960).

[17] [17a] An example from the literature [*Y. Hamasina, K. Tori*, and *A. Takamizawa*, Chem. Pharm. Bull. **13**, 1052 (1965)] related to the formation of **A** from **9** is the following:



[17b] Also in the case of the alkaline hydrolysis of carboxylic α-haloalkyl esters a mechanism ($B_{AC}2$ type) identical to the one postulated for the formation of **A** from **9** is operating, see *E. K. Euranto* in The Chemistry of Carboxylic Acids and Esters (*S. Patai*), p. 577, Wiley, New York, N.Y. 1969.

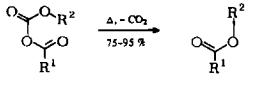
[18] In analogy to the following intermolecular reaction ⟨*E. H. Man, J. J. Sanderson*, and *C. R. Hauser*, J. Am. Chem. Soc. **72**, 847 (1950); *H. Henecka* in Methoden der organischen Chemie (*Houben-Weyl-Müller*), 4th. ed, Vol. 8, p. 555, Thieme, Stuttgart 1952; *Union Carbide Corp.* (Inv. *L. W. McTeer*), US-Pat. 2866813 (Dec. 30, 1958) [Chem. Abstr. **53**, P 9063b (1959)]⟩:



[19] The acetic acid-catalyzed conversion of **A** to **10**, postulated for the formation of **10** from **9**, was considered not to be a limiting factor for the obtainment of **7**, being plausible to assume that the acid-catalyzed reaction **A** → **10** is actually a reversible one, even though essentially displaced towards formation of **10**. This reversibility finds also an analogy in the case of aldehyde diacetates which, at high temperatures, are partially cleaved back to their precursor (aldehyde and acetic anhydride) under formation of acetic acid (a by-product) as well, see for example *F. W. Semmler*, Ber. Dtsch. Chem. Ges. **42**, 1161 (1909); *M. F. Shostakovskii, N. V. Kuznetsov*, and *Che-Min Yang*, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk **1962**, 710 [Chem. Abstr. **57**, 16389a (1962)].

[20] For the formation of **B** from **A** and acetic anhydride by acid or metal acetate catalysis cf.[18] and *F. W. Semmler* in note[19], respectively.

[21] For the decarboxylation of **B** to **7** cf. *T. B. Windholz*, J. Org. Chem. **25**, 1703 (1960), where the



R^1 = primary alkyl; $ArCH_2$
R^2 = primary or secondary alkyl; Ph

reaction is favoured by the presence of an acid catalyst or of an electron releasing R^2 group like isopropyl. This latter factor makes more plausible a decarboxylation at the stage of **B** rather than **A**, where the polarization of the aldehydic group imparts to the substituent a

marked electron attracting character. This hypothesis is substantiated, moreover, by the experimental result of the acetoxylation of **9** in the absence of acetic anhydride (see above), where the main reaction product was **10** rather than the decarboxylation product of **A** (acetoxyacetaldehyde).

[22] Cf. *F. W. Semmler* in note [19].

[23] For the spontaneous rearrangement of **4** to chloroacetaldehyde see [7b]. For the conversion of said aldehyde to E cf. [18].

[24] *R. K. Summerbell* and *L. K. Rochen*, J. Am. Chem. Soc. **63**, 3241 (1941).

[25] *E. Späth* and *L. Raschik*, Monatsh. Chem. **76**, 65 (1946).

[26] *L. D. Hall*, Carbohydr. Res. **4**, 429 (1967).

[27] *E. I. du Pont de Nemours and Co.* (Inv. *J. E. Castle* and *V. J. Webers*), US-Pat. 2768973 (Oct. 30, 1956) [Chem. Abstr. **51**, P 15556i (1957)].

[28] *E. Heuser* in Methoden der organischen Chemie (*Houben-Weyl-Müller*), 4th. ed., Vol. 2, pp. 458–459, Thieme, Stuttgart 1953.

[29] Quantitative GC determination of **5** was not possible since this aldehyde gave an ill-defined, unreproducible peak.

[30] Titrimetric dosage (hydroxylamine hydrochloride method [28]) of **5** in the neutralized hydrolysis solutions was unreliable since GC analysis revealed the presence, in these solutions, of chloroacetaldehyde (rearrangement product of **4** [7b]) as well.

[31] *N. A. Milas*, *S. Sussman*, and *H. S. Mason*, J. Am. Chem. Soc. **61**, 1844 (1939).

[32] *P. N. Rylander* in Organic Syntheses with Noble Metal Catalysts, Organic Chemistry, a Series of Monographs (*A. T. Blomquist* and *H. Wasserman*), Vol. 28, pp. 121–124, Academic Press, New York, N.Y. 1973.

[33] *G. Braun* in Organic Syntheses, Coll. Vol. 1 (*H. Gilman*), pp. 431–434, Wiley, New York, N.Y. 1941.

[34] *H. M. Teeter* and *E. W. Bell* in Organic Syntheses, Coll. Vol. 4 (*N. Rabjon*), pp. 125–127, Wiley, New York, N.Y. 1963.

[35] For IR spectra of cyclic carbonates see *J. L. Hales*, *J. Idris Jones*, and *W. Kynaston*, J. Chem. Soc. **1957**, 618.

[36] *M. F. Shostakovskii* et al. in note [19].

[37] This technique, though it necessitated a large amount of solvent to dissolve all of the **14** present, turned out to be the more selective of the ones tried.

[38] The addition, in this case, of ammonium chloride was not necessary since the latter was formed *in situ* from the excess of ammonia and the hydrogen chloride liberated in the hydrolysis of **4**.

[89/78]