Studies on beta-Lactams

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Since the discovery 1 of the activating effect of the N-(p-Nitro-phenyl)-group on the methine hydrogen of halogenacetamino esters, it has been found that the p-Acetyl-phenyl and m-Nitro-phenyl groups exert a similar effect. It has been shown that the delocalisation of the N-non-bonded hydrogen of halogenacetamino esters occurred in poor yields even in the presence of sodium ethoxide 10, while the base of choice in the above systems, and the effect of the bulk of the A-Aryl substituent is relegated to a minor position.

Discussion

After the presence of the beta-lactam ring and its biological significance was established in Penicillin 1, Cephalosporin and Padyshandera Terminalis 2, 3, several new methods were developed for its synthesis 4. Among these, the intra-molecular alkylation of N-substituted halogen acetamino malonates seemed to be the most general 5, 6. The technique of Sheehan and Bose was extended by Chatterjee and Rao, to systems in which the methine hydrogen atom was activated by groups other than two ester functions 7-9. It was noted that the closely related intra-molecular alkylation of o-halogen-alkylmalonic esters occurred in poor yields even in the presence of sodium ethoxide 10, while the base of choice in the Bose Sheehan synthesis was triethylamine.

References

5 J. C. Sheehan and A. K. Bose, J. Amer. chem. Soc. 72, 5158 [1950].
6 J. C. Sheehan and A. K. Bose, J. Amer. chem. Soc. 73, 1261 [1951].
10 H. N. Walborsky, J. Amer. chem. Soc. 71, 2941 [1949].
The effect of the group attached to the nitrogen atom of the halogen-acetamino esters had not attracted much attention until it was demonstrated that an \(N\)-(p-nitro-phenyl)-group exerted a long range activating influence on the methine hydrogen atom of such systems\(^\text{11}\).

A large number of compounds were investigated, using various bases:

\[
\begin{align*}
\text{A} & \quad \text{N-CH}_2\text{COOC}_2\text{H}_5 \\
\text{O=C-CH}_2\text{Cl} & \\
\text{B} & \\
\text{L} & \\
\end{align*}
\]

\[
\begin{align*}
\text{A} & \quad \text{N-C}_2\text{H}_5 \\
\text{O=C-CH}_2\text{Cl} & \\
\text{B} & \\
\text{L} & \\
\end{align*}
\]

The work indicated that in such systems, the \(N\)-Phenyl substituent was co-planar with the three valences of nitrogen and with the amide carbonyl of the halogen acetamino-ester and also with the beta-lactam carbonyl after cyclisation. A \(p\)-nitro-phenyl substituent on the nitrogen of such a halogenacetamino ester greatly activated the methine hydrogen atom, but when the co-planarity was disturbed as for example in the series (a) or (b) with bulky \textit{ortho}-substituents, then the activation decreased markedly.

The conclusion was that in the systems (1) the two functions attached to the carbon atom carrying the methine hydrogen atom, played their role in effecting cyclisation, together with the contributing activating effect from the \(N\)-substituent, to give the beta lactams (4).

In the work to be described attention has been centered on firstly, whether groups other than the nitro-group can cause activation to any marked degree; secondly whether an electron withdrawing substituent in the \textit{meta}-position can cause activation; and finally to establish the role of the \(N\)-aryl substituent as a whole more exactly.

The amino esters that were synthesised for the study had satisfactory IR absorption characteristics, and were characterised by microanalysis in addition (Table 1, Compounds 2). Liquids were purified and used directly for the next step as they could not be obtained analytically pure.

The esters could all be chloroacetylated by refluxing them with chloroacetyl chloride in benzene for several hours\(^\text{12}\).

The following halogen-acetamino esters were synthesised (Table 2), by this method. They were mostly liquids, which were purified preliminarily and used for the next step, while two were converted to their 2,4-DNPH derivatives\(^\text{13}\), which could be microanalysed.

\[
\begin{align*}
\text{A} & \quad \text{NH} \\
\text{B} & \\
\text{C} & \\
\text{D} & \\
\text{L} & \text{COOC}_2\text{H}_5
\end{align*}
\]

<table>
<thead>
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<tbody>
<tr>
<td>a</td>
<td>(\text{CH}_3\text{CO})</td>
<td>(\text{H})</td>
<td>(\text{H})</td>
<td>(\text{COOC}_2\text{H}_5)</td>
<td>91–92</td>
<td>Isopropanol</td>
</tr>
<tr>
<td>b*</td>
<td>(\text{CH}_3\text{CO})</td>
<td>(\text{H})</td>
<td>(\text{H})</td>
<td>(\text{Ph})</td>
<td>144–45</td>
<td>Isopropanol</td>
</tr>
<tr>
<td>c</td>
<td>(\text{CH}_3\text{O})</td>
<td>(\text{H})</td>
<td>(\text{H})</td>
<td>(\text{COOC}_2\text{H}_5)</td>
<td>57–58</td>
<td>Isopropanol/petroleum</td>
</tr>
<tr>
<td>d</td>
<td>(\text{H})</td>
<td>(\text{CH}_3)</td>
<td>(\text{H})</td>
<td>(\text{COOC}_2\text{H}_5)</td>
<td>165–69/3 mm</td>
<td>—</td>
</tr>
<tr>
<td>e</td>
<td>(\text{H})</td>
<td>(\text{H})</td>
<td>(\text{NO}_2)</td>
<td>(\text{Ph})</td>
<td>77–78</td>
<td>Isopropanol</td>
</tr>
</tbody>
</table>

Tab. 1. * Methyl ester.


\(^\text{12}\) Deutsches Reich Patent 264527 and 293897.

With the weak base triethylamine in benzene solution, the compound \(N\)-(p-acetyl-phenyl)-N-chloroacetyl-2-phenyl-glycine methyl ester (3b) eliminated the elements of HCl to afford the corresponding beta-lactam (4b) as a pale yellow crystalline solid which showed the expected absorption peaks in its IR spectrum. The compound (3a), as expected, cyclised much faster than the corresponding \(N\)-phenyl-substituted ester.

As a result, it was demonstrated that the \(N\)-(p-acetyl-phenyl)-group also activated the methine hydrogen atom and that, therefore, in principle, any electron-withdrawing group substituted on the phenyl ring attached to the nitrogen atom of the halogenacetamino-esters would activate the methine hydrogen, if there was no steric disturbance of the co-planarity of the \(N\)-aryl substituent with the three valences of nitrogen.

Certain points of difference, and others of similarity, however, manifest themselves in the \(p\)-acetyl series, as compared to the \(p\)-nitro-series of compounds. Firstly, in the former, the elimination of HCl with triethylamine is slower than in the latter. This is in accordance with the widely acknowledged fact that the nitro-group has greater “electron withdrawing capacity” than the acetyl group. Another interesting dissimilarity is that the beta-lactam (4b) absorbs at 5.63 \(\mu\) (C = O, lactam) as against 5.5 – 5.55 \(\mu\) in the \(p\)-nitro-phenyl series, showing a greater stability of the lactam CO – N bond in the former relative to the latter. Surprisingly, in spite of this stability the beta-lactam (4b), formed in-situ from the halogen-acetamide (3b) is opened up in solution with Rexyn-201 (OH\(^{+}\)) to the corresponding amino acid 5:

![Chemical structure](attachment:image.png)

The amino acid \(N(p\)-acetyl-phenyl\)-\(\beta\)-carbomethoxy-\(\beta\)-phenyl-\(\beta\)-alanine (5) was recrystallised from 95% ethanol and characterised by its IR spectrum and microanalysis.

The beta-lactam (4a) derived from \(p\)-acetyl-anilino-malonate was a liquid and was characterised as a solid 2,4-DNPH derivative which showed satisfactory microanalytical characteristics.
The acetyl group in the beta-lactam 4a and 4b is an attractive group to exploit. In view of the biologically interesting properties of amino-thiazoles and the work done on them by Chatterjee and Moza, the acetyl group was converted into a thiazole ring. As distinct from the work of Chatterjee and Moza, who converted an acid function through the alpha diazo-ketone into an alpha halogeno-ketone, the acetyl group in 4a was brominated. The phenacyl bromide was treated in-situ with a slight excess of thiourea. 6 was generated by ammonia.

The activation produced by electron withdrawing para-substituents on the N-phenyl group of the systems under study and mentioned above, on the methine hydrogen atom of those systems, leads to the question of whether a strongly electron-withdrawing group in a meta position could also lead to an activation of the methine hydrogen. Here the planarity of the N-aryl-V-CO-system is not disturbed since the meta-position has little steric effect on the N substituents of the halogen acetamino ester.

Surprisingly, this system (3e) also cyclised with triethylamine, to give the desired beta-lactam. It appears that the role of the electron withdrawing substituent on the N-aryl group is merely to deplete the pi-orbitals of the aryl substituent of their normal electron density, and this in some way serves to enhance the acidity of the methine hydrogen atom, leading to cyclisation with weak bases, which without this depletion of the electron-cloud would not occur.

No specific commitment has yet been made as to whether the bulk of the N-aryl substituent played a role in the cyclisation of compounds (3) and analogs. The question of whether the driving factor in the beta-lactam synthesis developed by Sheehan and Bose was derived from the bulk of the N-aryl substituent (forcing the carbon atoms holding the hydrogen atom to be eliminated and the chlorine atom to within bond forming distance) or from the delocalisation of the N-non-bonded electrons into the N-aryl substituent was not clarified. A general rule is that the more heavily the small ring is substituted, the stabler it is, and that, as a corollary, heavily substituted small ring compounds are easier to synthesise than their unsubstituted analogs. Unfortunately this rule does not apply to the N-aryl substituent in beta-lactams. In order to demonstrate the minor effect of bulk, relative to the importance of N-lone-pair delocalisation, we examined the kinetics of elimination of three systems. We chose chloracetanilidomalonate as a reference system, while in one system (3e) the phenyl group was substituted by a p-methoxy group. In the third system the phenyl group carried an ortho-methyl substituent (3d). Clearly if bulk governed the stability (hence rate of cyclisation) then the fastest elimination would occur with the compound 3d, while if delocalisation played the key role then the decrease in order of the rate of elimination of HCl with base would be from chloracetanilidomalate, through

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Table 3. Kinetics of elimination of HCl from Compounds 3 in benzene with triethylamine at 30 °C using identical concentrations.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Conc.</th>
<th>Rate of elimination</th>
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<tr>
<td></td>
<td></td>
<td>Time %</td>
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<tr>
<td>3c (p-methoxy-substituent)</td>
<td>4 g/40 ml benzene</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 ml Et3N</td>
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<tr>
<td></td>
<td>3.8 g/38 ml benzene</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.8 ml Et3N</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.2 g/52 ml benzene</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.2 ml Et3N</td>
<td></td>
</tr>
<tr>
<td>3d</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Kinetics of elimination of HCl from Compounds 3 in benzene with triethylamine at 30 °C using identical concentrations.

Then we can rationalise the slow rate of elimination as being due once again to a greatly decreased delocalisation of the N-lone pair relative to chloracetanilidomalonate.

Therefore, as far as the N-aryl substituent is concerned its role in delocalisation of the N-lone pair is of far greater consequence in the Sheehan Bose Synthesis than its bulk, which must be considered as having been relegated to a role of secondary importance. The IR absorption of the beta-lactam carbonyl in the compounds 4c and 4d, occurred, as expected, at a higher wavelength than for beta-lactams in general. Thus 4d (the half ester of the dicarbethoxy azetidinone produced with triethylamine) showed a lactam C = O peak at 5.77 μ since the N-lone pair was “more available” for delocalisation into the π-orbitals of the lactam carbonyl.

The Table 4 shows the beta-lactams synthesised in the study. Those that were liquid were characterised as 2,4-DNPH.

Table 4. * Characterised as 2,4-DNPH.
rised by conversion to derivatives, and the dicarbethoxy beta-lactams produced from compounds 3e and 3d were characterised by saponification one of the two ester functions to free COOH, when the compounds could be well crystallised for analysis.

**Description of the Experiments**

All melting points are uncorrected and were taken in open capillaries using a Gallenkamp m.p. apparatus. The IR spectra have been recorded using a Perkin-Elmer Infraord.

**N-(p-acetyl-phenyl)-aminomalonic acid diethyl ester (2a):** 5 g p-aminoaceetophenone and 4.5 g (3.3 ml) diethyl bromomalonic ester were mixed intimately and incubated at 20 mm pr. and at a temp. of 70°C for 5 days to give on working out with benzene 4.0 g (100%) p-amino-acetophenone hydrobromide as insoluble crystals. The benzene extracts were washed successively with 2 N HCl solution, water and dried over anhydrous sodium sulfate, charcoaled and filtered. Distillation of the benzene solution on a water bath under slightly reduced pressure afforded 2.6 g (50%) 2a. Recrystallised from isopropanol in yellowish-brown needles m.p. 91 – 92°C.

C₁₅H₁₉NO₅ (293.0)
Calculated C 61.49 H 6.48 N 4.78,
Found C 61.08 H 6.85 N 5.12.
IR (Nujol) μ 2.95 (N – H); 5.7, 5.75 (CO, ester);
6.0 (CO, aromatic ketone).

**N-(p-acetyl-phenyl)-N'-chloroacetyl-aminomalonic acid diethyl ester (3a):** 5.45 g 2a and 5.00 ml chloroacetyl chloride were gently refluxed at 110 to 120°C for 4 hr. (or in 50 ml of benzene for 10 hr.), cooled and poured into 7 ml of ice cold isopropanol. The excess isopropanol was distilled and the residual oil was taken in ether, washed with potassium carbonate solution, water, treated with sodium sulfate (anhydrous)/charcoal, charcoaled and filtered. Distillation of the benzene solution as a water bath under slightly reduced pressure afforded 2.95 g (50%) 3a. Recrystallised from isopropanol in yellowish-brown needles m.p. 91 – 92°C.

C₁₇H₁₈ClNO₅S (389.0)
Calculated C 55.52 H 4.88 N 10.79,
Found C 56.30 H 5.26 N 10.67.
IR (Nujol) μ 2.9 (N – H); 5.65 (C = 0, β-lactam); 5.7, 5.75 (CO, ester); 6.15 (C = N).

**N-(p-acetyl-phenyl)-2-phenyl-glycine-methyl ester (2b):** 10 g of p-amino acetophenone and 9.0 g freshly synthesised methyl-2-bromo-phenylacetate (b.p. 123 to 125°C/15 mm.) on incubation at 60 – 70°C/40 Torr for 48 hours, gave on working out with boiling benzene 8.0 g (100%) p-amino-acetophenone hydrobromide and from the benzene filtrate after purification 8.0 g (80%) 2b as a yellow residue. Yellowish flakes, from isopropanol m.p. 144 – 145°C.

C₁₇H₁₆NO₃ (283.0)
Calculated C 72.08 H 6.01 N 4.94,
Found C 71.94 H 5.99 N 4.94.
IR (Nujol) μ 2.99 (N – H); 5.75 (C = 0, ester);
6.0 (C = 0, ar. ketone).

**N-(p-acetyl-phenyl)-N'-chloroacetyl-2-phenyl-glycine-methyl ester (3b):** 5.0 g 2b and 7 ml chloroacetyl chloride at 100 – 110°C/2.5 hr. gave when worked out as for 3a, 5.0 g (80%) 3b as a viscous brown oil. Characterised as the 2,4-DNPH derivative m.p. 226 – 227°C (ethyl acetate).

C₁₈H₁₈ClNO₅ (539.5)
Calculated N 12.97,
Found N 12.87.

**N-(p-acetyl-phenyl)-2-oxo-4,4'-dicarbethoxy-azetidine (4a):** 3.60 g 3a in 40 ml anhydrous benzene was treated with 9.0 ml of triethylamine and the mixture filtered after 24 hr. to give 1.4 g (100%) triethylamine hydrochloride. The benzene layer was washed free of base with 2 N HCl solution, then with water, dried over anhydrous sodium sulfate, treated with active charcoal filtered and distilled to yield 3.0 g (90%) 4a as a brown oil characterised by its 2,4-DNPH derivative, m.p. 182 – 183°C (ethyl acetate).

C₂₅H₂₉ClN₅O₅ (513.0)
Calculated N 13.65,
Found N 13.62.

N-{p-[5-(2-amino-thiazolyl)]-phenyl}-2-oxo-4,4'-dicarbethoxy-azetidine (6): 3.0 g 4a was dissolved in anhydrous ether (15 ml). To the solution 100 mg of anhydrous aluminium chloride were added followed by 0.5 ml bromine. The reaction mixture was kept at 0 – 5°C and stirred (15 min.) until the bromine color was discharged. The ether along with the HBr was quickly removed in a stream of dry air at 40°C. The oil left was treated with 3.5 g thiourea in 30 ml of methanol and the mixture refluxed for 3 hours. The methanol was distilled off and the crystalline residue left was dissolved in water and basified with strong ammonia solution added dropwise to yield 2.0 g (52%) 6 as a yellow powder. Needles from isopropanol m.p. 199°C.

C₁₈H₁₈N₅O₄ (323.0)
Calculated C 70.60 H 5.27 N 10.67,
Found C 70.96 H 5.76 N 4.30.
IR (Nujol) μ 5.63 (C = 0, beta lactam); 5.7 (C = 0, ester); 5.92 (C = 0, Ar. ketone).
N-(p-acetyl-phenyl)-β-phenyl-β-carbethoxy-β-alanine (5): 0.90 g of halogen acetamino ester 3 b, was dissolved in 25 ml of anhydrous methanol and stirred for 24 hr. with Rexyn-201 (OH -). The Rexyn was then filtered out, extracted twice with 25 ml methanol at the b.p., the filtrates added and stripped to yield 350 mg (43.6%) of 5 as an oil which crystallised on standing under petroleum/isopropanol, m.p. 174—175° (methanol).

N-(m-nitro-phenyl)2-phenyl-glycine-ethyl ester (2e): Incubation of 9.2 g meta-nitro aniline and 8.1 g ethyl bromomalonic ester were made homogeneous by gentle warming, cooled quickly to 30 °C and then evacuated to 15 Torr. The mixture warmed up and was kept cooled for 24 hr. with Rexyn-201 (OH -). The Rexyn was then dissolved in 25 ml of anhydrous methanol and stirred for 1 hour the flask was added 3.85 ml triethylamine and stirred in a stoppered Erlynmeyer flask. This was followed by addition of 50 ml of anhydrous ether, the precipitated potassium salt was filtered out, dissolved in 10 ml of water chilled to 5 °C and acidified with 12 N HCl when the free acid 4 e was deposited as an oil.

The oil was then filtered out, extracted twice with 25 ml methanol at the b.p., the filtrates added and stripped to yield 350 mg (43.6%) of 5 as an oil which crystallised on standing under petroleum/isopropanol, m.p. 174—175° (methanol).

C_{19}H_{13}NO_{5} (341.0)
Calculated C 67.10 H 5.85 N 4.15,
Found C 67.58 H 5.83 N 4.42.
IR (Nujol) μ 2.93 (N—H); 3.73 (O—H); 5.69 (C=O, ester); 5.78 (C=O, acid); 6.03 (C=O, aromatic ketone).

N-(p-methoxy-phenyl)-N-chloroacetyl-amino-malonic acid diethyl ester (3 c): 4.0 g 2 c, in 30 ml benzene, with 2.8 g chloroacetic acid and 1.8 ml PCl_5, 4.5 g triethylamine to completion and filtered to give in total 8.5 g (84%) p-anisidine hydrobromide and 10.0 g (70%) 2 c as brownish colorless crystals m.p. 57—58°.

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IR (Nujol) μ 2.93 (N—H); 3.73 (O—H); 5.69 (C=O, ester); 5.78 (C=O, acid); 6.03 (C=O, aromatic ketone).

N-(o-methyl-phenyl)-2-oxo-4,4'-dicarbethoxy-azetidine (2 c): Amidification of 5.0 g 2 d in 25 ml benzene, with 2 g chloroacetic acid and 2 ml phosphorous trichloride, gave on working out the solution in the usual manner, 5.2 g (75%) 3 d as a pale green fluorescent oil.

IR (Nujol) μ 2.9 (N—H); 5.7, 5.75 (C=O, ester).

N-(o-methyl-phenyl)-N-chloroacetyl-amino-malonic acid diethyl ester (3 d): Saponification to 4 d: 3.38 g N-(o-methyl-phenyl)-2-oxo-4,4'-dicarbethoxy-azetidine was dissolved in 20 ml ethanol using 0.65 g potassium hydroxide for two hours. The precipitated potassium salt (after ether addition) was worked out as for 4 e to give the half ester N-(o-methyl-phenyl)-2-oxo-4-carbethoxy-4'-carboxyazetidine 4 d as an oil which solidified by tituration under light petroleum at 5 °C. Yield 1.4 g (41.7%). Very pale yellow needles from benzene/petroleum m.p. 118—119°.

C_{14}H_{12}NO_{6} (293.0)
Calculated N 4.77,
Found N 4.43.
IR (Nujol) μ 3.85 (broad, O—H, carboxylic); 5.6 (C=O, beta-lactam); 5.7 (C=O, ester); 5.9 (C=O, acid).

N-(o-methyl-phenyl)-2-oxo-4,4'-dicarbethoxy-azetidine: 5.2 g halogen acetamino ester 3 d in 52 ml anhydrous benzene was stirred with 5.2 ml triethylamine in a stoppered Erlynmeyer flask. The solution was filtered every two hours to keep track of the elimination (Table 3), the solution boiled with two ml excess triethylamine to completion and filtered to give in total 2.093 g (100%) triethylamine hydrochloride. Working out the benzene filtrate afforded the liquid beta lactam; 4.4 g (95%); as a white oil.

Saponification to 4 d: 3.38 g N-(o-methyl-phenyl)-2-oxo-4,4'-dicarbethoxy-azetidine were saponified in 20 ml ethanol using 0.65 g potassium hydroxide for two hours. The precipitated potassium salt (after ether addition) was worked out as for 4 e to give the half ester N-(o-methyl-phenyl)-2-oxo-4-carbethoxy-4'-carboxyazetidine 4 d as an oil which solidified by tituration under light petroleum at 5 °C. Yield 1.4 g (41.7%). Very pale yellow needles from benzene/petroleum m.p. 118—119°.
alpha-bromo phenylacetate for 4 days at 70 — 80 °C/40 Torr. gave on working out with chloroform, 10 g (100%) 2e from chloroform and 7.2 g (100%) m-nitro aniline hydrobromide. 2e from isopropanol gave yellow-orange needles, m.p. 77 — 78°C.

C₁₈H₇₈O₂N₂Cl (376.5)
Calculated N 7.44,
Found N 7.80.
IR(Nujol) µ 5.74 (C = O, ester); 5.84 (C = O, amide).

N-(m-nitro-phenyl)-2-oxo-4-phenyl-4'-carbethoxy-azetidine (4e): 2.1 g 3e, in 35 ml dry benzene, stirred for 18 hr. with 10 ml triethylamine to give on filtration triethylamine hydrochloride corresponding to 66% elimination. The filtrate was refluxed to complete the elimination, and working out the benzene solution afforded 1.7 g (90%) 4e as a yellow oil, which solidified on standing, m.p. 93 — 94° (95% ethanol).

The authors wish to express their highest sense of gratitude to Professor AJAY K. Bose of Steven's Institute of Technology, New Jersey, USA for his invaluable help in arranging the IR spectra of so many compounds to be taken. We also wish to thank Dr. MAGAR S. MANHAS of the same Institute. We are obliged to Dr. JAN TROJANEK of the Research Institute of Natural Drugs in Prague, Czechoslovakia for his help in the microanalysis, as well as Dr. H. P. S. CHAWLA and Dr. V. V. RAO of the Central Drugs Research Institute in Lucknow-India. We acknowledge the help provided by the National Chemical Laboratory-Poona for some of the micro-analyses.

Eine Synthese der A-Kette des Schafinsulins unter ausschließlicher Verwendung säurelabiler Schutzgruppen

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