(7) P. E. Peterson, J. P. Wolf, III, and C. Niemann, *J. Org. Chem.*, **23**, 303 (1958).
(8) Formation of oxazole from the corresponding acyl-substituted isonitrile has been well investigated. See I. J. Turchi and M. J. S. Dewar, *Chem. Rev.*, **75**, 389 (1975).
(9) T. Miki and T. Matsuo, *Yakugaku Zasshi*, **91**, 1030 (1971).
(10) The benzo analogues of the compound (**9**) were prepared recently by pyrolysis of 2-(2-azidobenzoyl)pyridines. See R. Y. Ning, W. Y. Chen, and L. H. Sternbach, *J. Heterocycl. Chem.*, **11**, 125 (1974).
(11) The chemical shift of the 2-methine proton in 1-azirine derivatives is in the range of δ 9.6–10.2. See ref 4b and 5e.
(12) W. Bauer and K. Hafner, *Angew. Chem.*, **81**, 787 (1969).
(13) (a) R. Huisgen, H. Konig, G. Binsch, and H. J. Sturm, *Angew. Chem.*, **73**, 368 (1961); (b) R. Huisgen, *ibid.*, **75**, 604 (1963).
(14) D. Knittel, H. Hemetsberger, R. Leipert, and H. Weidmann, *Tetrahedron Lett.*, 1459 (1970).
(15) However, thermal process of 2-unsubstituted azirine to the corresponding isonitrile was also proposed in the isomerization of indoxazene to benzoxazole. See J. P. Ferris and F. R. Antonucci, *J. Am. Chem. Soc.*, **96**, 2014 (1974).
(16) (a) R. C. Shah and M. B. Ichaporia, *J. Chem. Soc.*, 431 (1936); (b) H. M. Blatter and H. Lukaszewski, *Tetrahedron Lett.*, 855 (1964).
(17) Contaminated with isonitrile **10a**.

Synthesis of C_7 Alkylated 7-Deaminocephalosporin Derivates

J. S. Wiering and Hans Wynberg*

Department of Organic Chemistry, The University, Zernikelaan, Groningen, The Netherlands

Received November 24, 1975

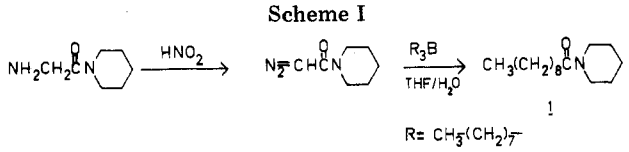
Several 7-alkyl cephalosporins lacking the 7-amino function have been prepared by treatment of the 7-diazo derivatives of cephalosporanic acid *tert*-butyl esters with a variety of trialkylboranes and a dialkylborane. Mixtures of α- and β-substituted cephalosporin *tert*-butyl esters were formed. These were hydrolyzed to the free acids. Biological screening of the free acids (as α and β mixtures) showed little or no antimicrobal activity except for the 7-methyleneadamantyldeacetoxycephalosporanic acid. A new, very mild method of oxidation of the sulfur atom in the cephalosporins was discovered. Sulfoxides were isolated from the alkylation reaction.

In recent years intensive research has been carried out in order to obtain modified cephalosporins with improved properties.[1] Several groups have attempted modifications at the C_7 positions of cephalosporins.[1b,2] As far as we know no cephalosporins[3] are known in which the 7-amino function has been replaced by an alkyl or functionalized alkyl group.[3] By introducing such alkyl groups the lipophilic character of the molecule, and consequently its penetrating ability[4] into the cell wall, changes. The purpose of the research reported here was to synthesize alkylated cephalosporins lacking the amino function at the β-lactam C_7 carbon, and to determine the effect of this change on biological activity.

Results and Discussion

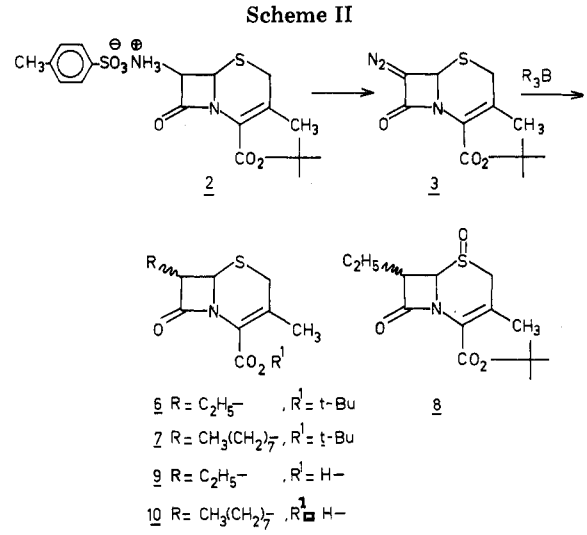
In order to introduce an alkyl side chain at C_7, in fact the replacement of an amino by a methylene group, we made use of the reaction of trialkylboranes with diazo esters,[5a] a reaction which we found to be applicable to diazo amides also. For example, the reaction of trioctylborane with 1-(α-diazoglycyl)piperidine in aqueous tetrahydrofuran gave the amide 1 in almost quantitative yield[6] (Scheme I).

Scheme I



The diazotization of the *p*-toluenesulfonic acid salt of 7-aminodeacetoxycephalosporanic acid *tert*-butyl ester (**2**, Scheme II) and 7-aminocephalosporanic acid *tert*-butyl ester (**4**, Scheme IV) was carried out in a mixture of methylene chloride and water.[8] It was possible to isolate the diazo cephem **3** in 80% and **5** in 60–80% yield. Both compounds are yellow, crystalline solids, of which **5** could be obtained analytically pure. The alkylation of **3** with triethyl- and trioctylborane was only successful within a temperature range from −40 to −80 °C (Scheme II). At temperatures higher than −40 °C, no products with intact β-lactam ring were formed. The amount of water was of crucial importance to the course of the reaction.[5] With more than 30 equiv of water, based on diazo cephem **3**, no β-lactam containing products could be isolated. With 20–30 equiv of water, sulfoxide **8** was formed. It could be shown that the latter was not produced during oxidative work-up.

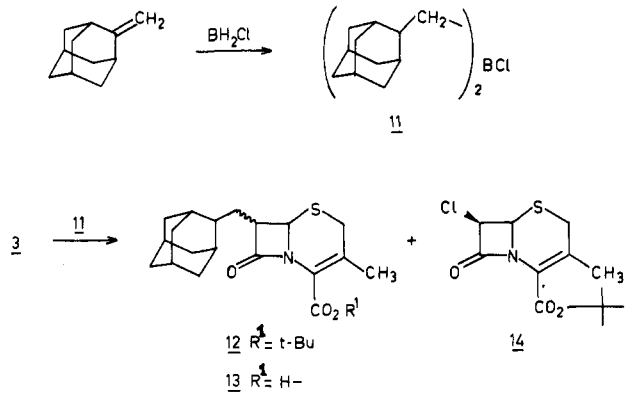
Scheme II



Using minor amounts of water (5–20 equiv) a mixture of **6** and **8** was formed, while alkylation in the presence of 1–5 equiv of water gave the cephem ester **6** as the sole product. The alkylated cephem esters **6** and **7** are both relatively unstable liquids and difficult to purify. Treatment of **6** and **7** with trifluoroacetic acid afforded the acids **9** and **10**, which are stable for a few days at −20 °C.

Diborane reacts with alkenes containing bulky groups to the dialkylborane stage only.[7] Since dialkylmonochloroboranes with bulky alkyl groups react rapidly with diazo esters,[9] we used monochloroborane as reagent to transform methyleneadamantane into the dimethyleneadamantylmonochloroborane **11**. Alkylation of **3** with **11** gave two products **12** and **14**, in the statistical ratio 2:1[10] (Scheme III). The products were separated by repeated chromatography.

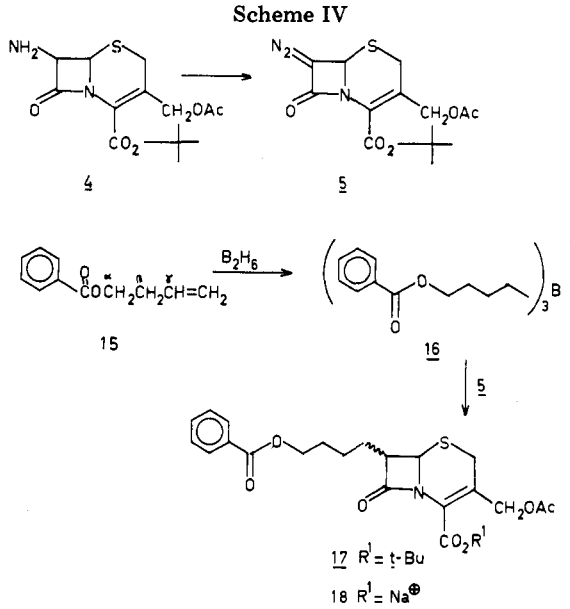
Scheme III



7-*epi*-Chlorodeacetoxycephalosporanic acid *tert*-butyl ester (**14**) was identical with the compound that was formed by treating **3** with hydrochloric acid in tetrahydrofuran. Treatment of **12** with trifluoroacetic acid afforded the acid **13** in 85% yield.

In introducing a functionalized alkyl group at the C_7 position we were restricted in the choice of the appropriate substituted alkenes. First, diborane may react with the double bond, with a functional group in the alkene, or with both.[11] Second, the addition at the double bond is influenced by directing effects caused by the functional group.[12,13] 3-Butenyl benzoate (**15**) was treated with diborane to give tri(4-benzoyloxybutyl)borane (**16**). Reaction of **16** with 7-diazocephalosporanic acid *tert*-butyl ester (**5**) gave the C_7 alkylated cephem ester **17** (Scheme IV). Al-

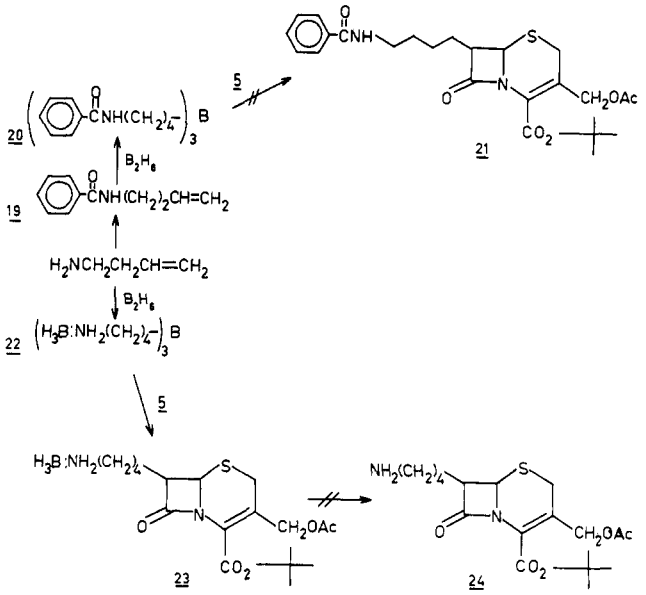
Scheme IV



though alkaline hydrogen peroxide oxidation–hydrolysis[10] of **16** revealed 15% addition of the boron at the γ carbon atom of **15**, no alkylated cephem ester could be detected which was formed by migration of this secondary alkyl group from boron to the C_7 carbon atom. Treatment of the ester **17** with trifluoroacetic acid gave the alkylated cephalosporanic acid **18**, which was isolated as the sodium salt.

The same procedure was not successful for introduction of the *N*-butylbenzamide group (Scheme V). Treatment of diazo cephem ester **5** with 2.5 equiv of tri[4-(*N*-benzoyl)-butylamino]borane (**20**) gave no alkylated cephem ester **21**, but we recovered 50% diazo compound **5**, after separating

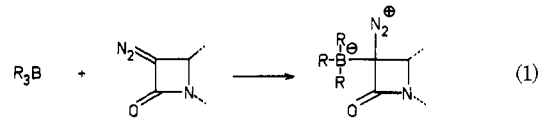
Scheme V



the latter from the alcohols[14] formed during the oxidative work-up from borane **20**. We believe that chelate ring formation between the amide nitrogen and the boron atom in **20** reduces the Lewis acid character of the borane and prevents alkylation.

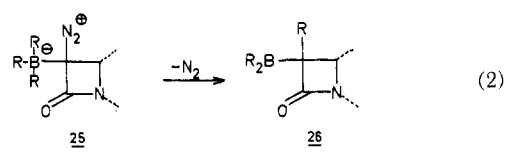
To circumvent this problem an alternative approach was tried, in which the trialkylborane **22** reacts with **5** to give **23**. Aqueous hydrochloric acid in tetrahydrofuran[11] was needed to hydrolyze the amine–boron hydride complex to the free amine; however, no **24** or any other compound with an intact β-lactam ring was formed. Apparently the β-lactam does not survive these hydrolysis conditions. The alkylation of the diazo cephem esters **3** and **5** gave rise to a mixture of two alkylated products with cis and trans configuration at the 6 and 7 position of the β-lactam ring. This ratio could easily be estimated with NMR spectroscopy, by integration of the two doublet signals of the C_6 proton, cis J = 5 Hz and trans J = 2.5 Hz, which are separated by 30 Hz. The data are summarized in Table I. Deblocking of the *tert*-butyl esters with trifluoroacetic acid does not affect this cis–trans ratio. The presence of the Δ_3 cephem nucleus was confirmed by the remaining NMR data.

No detailed study has been published about the mechanism of the reaction of trialkylboranes with diazo compounds, but it appears likely that the reaction involved first a coordination of the borane with the diazo compound to produce the quaternary boron intermediate **25** (eq 1).



(1)

This is followed by loss of nitrogen from **25** with either subsequent or concurrent migration of an alkyl moiety (eq 2).



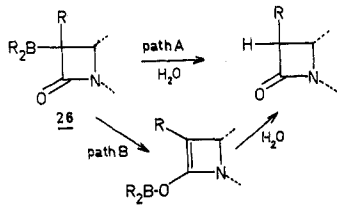
(2)

Hydrolysis of intermediate **26** with water gives the desired product (eq 3, path A). Alternatively, it is possible that in-

Table I

Compd	Yield, %	Cis, %
6	90	33
7	80	30
8	22	33
9	90	33
10	85	30
12	31	6
13	85	6
17	85	~2
18	85	~2

termediate **26** exists in the isomeric enol–borinate form[15] (path B), which is rapidly hydrolyzed to the product.

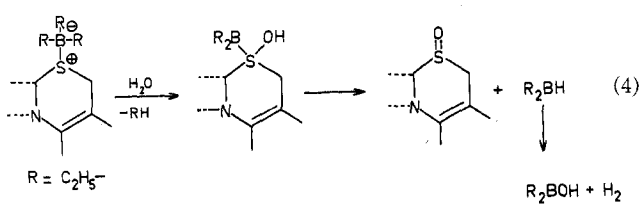


(3)

In cephalosporins the thermodynamically more stable form is the trans-substituted β-lactam ring, probably because the 7 substituents are more crowded in the β than in the α configuration.[16] The α side of the molecule is the least hindered side. Thus the main product in the addition of the trialkylboranes to the diazo cephems **3** and **5** should be the α-substituted alkyl cephalosporin. Neither kinetic nor thermodynamic control appears to be able to influence this result. This is in fact the case. Using trialkylboranes with bulkier alkyl groups (Table I), we found an increasing formation of the trans-substituted cephalosporins. Until now we have been unsuccessful in changing the cis–trans ratio in favor of the cis epimer, the latter in all probability being the configuration which may show biological activity.[17,18]

Formation of the cephem sulfoxide **8** seems to be the first example of oxidation of sulfur with a trialkylborane–water mixture.

We believe that it is the addition complex of sulfur with the trialkylborane that reacts with water (eq 4). Hydrogen gas was shown to be present by GLC.



(4)

The alkylated cephalosporins described here were tested for antimicrobial activity in vitro. The cis–trans mixtures were tested as such, because we were unable to separate the isomers. Only the methyleneadamantyldeacetoxycephalosporanic acid showed a low but definite activity against some gram-positive organism. Minimum inhibitory concentration (MIC) values: *Streptococcus haemolyticus*, 12.5; *Sarcinea lutea*, 6.5; *Haemophilus suis*, 50.

Experimental Section

The ^1H NMR spectra were determined on a Varian T60 spectrometer. Chemical shifts are relative to Me_4Si. Infrared spectra were recorded on a Perkin-Elmer 125 or 257 and Unicam Sp200. The mass spectra were obtained on a AEI MS 902 mass spectrometer. Column chromatography was carried out on aluminum oxide "activ neutral" from Merck and silica gel 60–120 mesh from BDH. Merck silica gel PF 254 was used for preparative thin layer chromatography. Melting points are uncorrected. Tetrahydrofuran was freshly destilled from $LiAlH_4$ under a nitrogen atmosphere. We thank the Squibb Institute for Medical Research for a generous supply of 7-ADCA and some financial support to one of us (J.S.W.).

1-Glycylpiperidine. A solution of 9.5 g (3.4 mmol) of 1-(*N*-benzyloxycarbonylglycyl)piperidine[19] in 100 ml of methanol was hydrogenolyzed in the presence of 900 mg of 10% palladium on carbon at room temperature and atmospheric pressure until the uptake of hydrogen had ceased. The solution was evaporated to 25 ml and the catalyst was removed by centrifugation. Evaporation to dryness in vacuo gave 5 g of colorless oil, which was distilled to give 4.6 g (3.2 mmol, 95%) of 1-glycylpiperidine: bp 84–85 °C (3 mmHg); ir (neat) 3400, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.3–1.7 (8 H), 3.2–3.6 (6 H). Anal. Calcd for $C_7H_{14}N_2O$: C 59.07; H, 9.93; N, 19.71. Found: C, 59,13; H, 9.93; N, 19.35.

1-(α-Diazoacetyl)piperidine. A solution of 500 mg (3.52 mmol) of 1-glycylpiperidine in 20 ml of $CHCl_3$ was refluxed during 15 min with 540 mg of isoamyl nitrite and 720 mg of acetic acid. The yellow solution was diluted with 20 ml of $CHCl_3$, cooled, and washed with 5 ml of 1 N H_2SO_4, 5 ml of water, 5 ml of saturated aqueous $NaHCO_3$, and twice with 5 ml of water. After drying (Na_2SO_4) and evaporation to dryness in vacuo, the yellow residue was purified by column chromatography on aluminum monoxide activity III, using ether as eluent. 1-(α-Diazoacetyl)piperidine was isolated as a yellow oil (400 mg, 2.6 mmol, 70%): ir (CH_2Cl_2) 2180, 1600 cm^{-1}; NMR ($CDCl_3$) δ 5.2 (3 H), 3.1–3.4 (4 H), 1.2–1.7 (6 H).

1-Caprylpiperidine (1). To a solution of 0.35 mmol of trioctylborane[20] in 9 ml of dry THF was added 0.1 ml of water and 46 mg (0.30 mmol) of 1-(α diazoacetyl)piperidine. After 3 h at 35 °C 1 ml of 30% hydrogen peroxide was added and the colorless solution was washed with brine solution (3 × 5 ml). GLC analysis indicated 92% yield of **1**. Isolation was carried out with preparative GLC, column 6 ft × 0.5 in. SE-30: $n^{20}D$ 1.4720; ir (CH_2Cl_2) 1630 cm^{-1}; NMR ($CDCl_3$) δ 0.85 (3 H), 1.55 (14 H), 1.65 (6 H); 2.20 (2 H), 3.3 (4 H). Compound **1** was identical in all aspects with an authentic sample.

***p*-Toluenesulfonic Acid Salt of 7-Aminodeacetoxycephalosporanic Acid *tert*-Butyl Ester (2).** To 1.35 g (5 mmol) of 7-aminodeacetoxycephalosporanic acid *tert*-butyl ester[2b] in 50 ml of ether was added a solution of 1.0 g (1.1 equiv) of *p*-toluenesulfonic acid monohydrate in 5 ml of ether and 5 ml of THF. The salt **2** precipitated immediately. After standing in the cold for 1 h the salt was isolated and recrystallized from hot acetonitrile to give 2.1 g (95%) of white salt **2**: mp 175.5 °C dec (preheated block); ir (Nujol) 3200–2600, 1670, 1620, 1650, 1600, 1540 cm^{-1}. Anal. Calcd for $C_{19}H_{26}N_2S_2O_6$: C, 51.56; H, 5.92; N, 6.33; S, 14.49. Found: C, 51.02; H, 5.95; N, 6.06; S, 14.15.

7-Diazodeacetoxycephalosporanic Acid *tert*-Butyl Ester (3). A mixture of 265 mg (0.6 mmol) of compound **2**, 1.5 g of sodium nitrite, 60 ml of $CHCl_2$, and 60 ml of ice water was stirred vigorously and cooled in an ice bath. After 5 min 180 mg (0.95 mmol) of *p*-toluenesulfonic acid monohydrate was added to this mixture gradually over a period of 20 min and stirring was continued for 10 min. The yellow mixture was transferred to an ice-cold separatory funnel and the organic layer was washed twice with 10-ml portions of brine solution. After drying (Na_2SO_4) and evaporation in vacuo to dryness, the residual yellow oil was purified by column chromatography on 6 g of aluminum oxide activity III with CH_2Cl_2 as eluent. Evaporation gave the diazocephem ester **3**, as a yellow oil which solidified: mp 42–43 °C dec; ir (CH_2Cl_2) 2090, 1760, 1700, 1260 cm^{-1}; NMR ($CDCl_2$) δ 5.6 (s, C_6 H), 3.31 (AB q, J = 10 Hz, C_2CH_2), 2.1 (s, CH_3), 1.5 (s, *t*-Bu).

7-Ethyldeacetoxycephalosporanic Acid *tert*-Butyl Ester (6). A three-necked 50-ml flask, equipped with two pressure-equalized dropping funnels and a thermometer, was flushed with nitrogen. The flask was charged with 5 ml of dry THF and cooled to −65 °C. One dropping funnel was filled with a solution of 113 mg (0.40 mmol) of diazo cephem ester **3** in 10 ml of dry THF. The second dropping funnel was filled with 0.8 ml (2 equiv) of 1.008 M triethylborane in THF, 10 ml of THF, and 0.03 ml of water. Both solutions were added at the same rate to the THF over a period of 5 min, keeping the temperature at −65 °C. The solution was allowed to come to −45 °C and 5 drops of 30% hydrogen peroxide was added. When the temperature had reached −15 °C, the mixture was washed in a separatory funnel with brine solution (3 × 7 ml). The almost colorless organic layer was cooled, diluted with 30 ml of CH_2Cl_2, and dried (Na_2SO_4). After evaporation to dryness, the residual oil was purified by column chromatography with 7 g of silica gel, deactivated with 0.8 ml of water, with CH_2Cl_2 as eluent. Evaporation of the first 30 ml gave 110 mg (0.38 mmol, 90%) of oil

6. Preparative thin layer chromatography with CH_2Cl_2–5% ether afforded analytically pure **6**: ir (CH_2Cl_2) 1770, 1720 cm^{-1}; NMR ($CDCl_3$) δ 4.84 (d, J = 5 Hz, C_6 H), 4.40 (d, J = 2.5 Hz, C_6 H), 3.30 (AB q, J = 18 Hz, C_2 CH_2), 3.5 (m, C_7 H), 3.08 (m, C_7 H), 2.05 (s, CH_3), 1.85 (m, $-CH_2-$), 1.55 (s, t-Bu), 1.15 (t, J = 7 Hz, CH_3); mass spectrum m/e 283, 255, 228, 199, 158, 157, 140, 139, 57. Anal. Calcd for $C_{14}H_{21}NSO_3$: C, 59.34; H, 7.47; N, 4.94; δ 11.31. Found: C, 58.92; H, 7.45; N, 4.82; δ 11.20. Uv λ_{max} (MeOH) 265 nm (ϵ 6600).

7-Ethyldeacetoxycephalosporanic Acid (9). Compound **6** (85 mg, 0.3 mmol) was stirred with 2.5 ml of trifluoroacetic acid during 5 min at room temperature. Evaporation in vacuo at 10^{-2} mmHg gave a light brown colored residue, which was triturated with dry pentane. After evaporation of the pentane, the solid was taken up in 1 ml of CH_2Cl_2 and dropped into 15 ml of dry ether. This solution was cooled for 30 min at −20 °C. A little brown solid was removed by centrifugation and the supernatant liquid was evaporated. The remaining solid was dissolved in 1 ml of CH_2Cl_2 and added with stirring to 50 ml of dry pentane. Compound **9** (63 mg, 0.27 mmol, 90%) was isolated as a pale yellow, amorphous solid: mp 70–78 °C; ir (CH_2Cl_2) 3600–2500, 1760, 1720, 1630 cm^{-1}; NMR ($CDCl_3$) δ 9.1 (s, COOH), 4.9 (d, J = 5 Hz, C_6 H), 4.45 (d, J = 2.5 Hz, C_6 H), 3.4 (AB q, J = 18 Hz, C_2 CH_2), 3.65 (m, C_7 H), 3.15 (m, C_7 H), 2.2 (s, CH_3), 1.9 (m, $-CH_2-$), 1.1 (~t, $-CH_3$, J = 7 Hz); mass spectrum calcd, m/e 227.061; found, m/e 227.054.

7-Ethyldeacetoxycephalosporanic Acid *tert*-Butyl Ester *S*-Oxide (8). To a solution of 0.4 mmol of triethylborane in 15 ml of dry THF under nitrogen atmosphere was added 0.35 ml of water. The mixture was cooled to −60 °C and 113 mg (0.4 mmol) of diazo cephem ester **3** in 10 ml of dry THF was added over a period of 10 min. The work-up procedure was the same as described for **6**. The isolated colorless oil was submitted to preparative silica gel thin layer chromatography using ether–CH_2Cl_2 (1:2) as eluent. Compound **8** was isolated as an oil (24 g, 0.08 mmol, 20%), which was crystallized from CH_2Cl_2–pentane as a white solid: mp 141–145 °C; ir (CH_2Cl_2) 1780, 1720, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.6 (d, J = 5 Hz), 4.2 (d, J = 2 Hz, C_6 H), 3.1–3.9 (C_2 CH_2, C_7 H), 2.05 (s, CH_3), 1.7–1.9 (m, $-CH_2-$), 1.5 (s, t-Bu), 1.0–1.3 (t, CH_3); mass spectrum calcd, m/e 299.119; found, m/e 299.118. Hydrogen was proved in the gas evolving from the reaction mixture by GLC, column 6 ft × 0.5 in., molecular sieves 5 Å, 80 °C.

7-Octyldeacetoxycephalosporanic Acid *tert*-Butyl Ester (7). The procedure for the preparation of **6** was followed, using trioctylborane as alkylating agent. Compound **7** was isolated in 80% yield after column chromatography on silica gel, deactivated with 10% water. Analytically pure material was obtained by preparative silica gel thin layer chromatography with CH_2Cl_2–5% ether as eluent: ir (CH_2Cl_2) 1770, 1715 cm^{-1}; NMR ($CDCl_3$) δ 4.88 (d, J = 5 Hz, C_6 H), 4.42 (d, J = 2.5 Hz, C_6 H), 3.30 (AB q, J = 18 Hz, C_2 CH_2), 3.5 (m, C_7 H), 3.18 (m, C_7 H), 2.1 (s, CH_3), 1.6 (s, t-Bu), 2.3 (octyl, 12 H), 1.0 (CH_3); mass spectrum m/e 367, 339, 283, 158, 157, 140, 139, 57. Anal. Calcd for $C_{20}H_{33}NSO_3$: C, 65.35; H, 9.05; N, 3.81; S, 8.72. Found: C, 65.04; H, 9.05; N, 3.85; S, 8.51. Uv λ_{max} (EtOH) 267 nm (ϵ 6600).

7-Octyldeacetoxycephalosporanic Acid (10). The procedure for the preparation of **9** was followed. Acid **10** was isolated as an oil in 85% yield: ir (CH_2Cl_2) 1760, 1720, 1630 cm^{-1}; NMR ($CDCl_3$) δ 9.0 (s, COOH), 4.90 (d, J = 5 Hz, C_6 H), 4.45 (J = 2.5 Hz, C_6 H), 3.4 (AB q, J = 18 Hz, C_2 CH_2), 2.2 (s, CH_3), 1.55 (m, $-CH_2-$), 1.3 (octyl, 12 H), 0.9 (CH_3). Determination of the exact mass was not possible, because the molecular ion peak was lacking in the mass spectrum.

7-Methyleneadamantyldeacetoxycephalosporanic Acid *tert*-Butyl Ester (12). A solution of 120 mg (0.43 mmol) of diazo cephem ester **3** in 10 ml of dry ether (distilled from $LiAlH_4$) and a freshly prepared solution of 2 equiv of borane **11** in 10 ml of dry ether were added at the same rate to each other, keeping the temperature at −80 °C. After 5 min 0.06 ml of MeOH was added, followed by about 1.5 ml of triethylamine to neutralize the mixture. After the mixture was allowed to come to −10 °C, the latter was washed with brine solution (3 × 5 ml). The organic layer was dried (Na_2SO_4) and evaporated to dryness in vacuo. By preparative silica gel thin layer chromatography with CH_2Cl_2 as eluent a mixture of **12** and **14** was isolated as an oil (114 mg). Repeated thin layer chromatography of this oil with benzene–acetone (9.75:0.25) gave 54 mg (0.13 mmol, 31%) of compound **12**, crystallized from $CHCl_3$–pentane: mp 160–165.5 °C; ir (CH_2Cl_2) 1760, 1710 cm^{-1}; NMR ($CDCl_3$) δ 4.8 (d, J = 5 Hz, C_6 H), 4.35 (d, J = 2 Hz, C_6 H), 3.28 (AB q, J = 18 Hz, C_2 CH_2), 2.0 (s, CH_3), 1.8 (methyleneadamantyl), 1.55 (s, t-Bu). Anal. Calcd for $C_{23}H_{33}NSO_3$: C, 68.62; H, 8.01; S, 7.97. Found C, 67.07; H, 8.13; S, 7.99. Mass spectrum exact mass calcd, m/e 403.218; found, m/e 403.218. At the same time 22 mg of compound **14** was isolated as an oil: ir (CH_2Cl_2) 1780, 1710 cm^{-1}; NMR ($CDCl_3$) δ 4.68 (d, J = 1.5 Hz, C_7 H), 4.58 (d, J = 1.5 Hz, C_6 H), 3.3 (AB q, J = 18 Hz, C_2 CH_2), 2.05 (s, CH_3), 1.5 (s, t-Bu); mass spectrum m/e 289/291 (2:1), 233, 235, 205, 207. The spectra of **14** were identical with the spectra of a sample prepared by treating diazo cephem ester **3** (100 mg) with 1 ml of concentrated HCl in 15 ml of THF at 0 °C during 3 min.

7-Methyleneadamantyldeacetoxycephalosporanic Acid (13). Compound **12** (40 mg, 0.22 mmol) was stirred with 0.8 ml of trifluoroacetic acid at room temperature during 5 min. Evaporation gave a light yellow syrup, which was crystallized from CH_2Cl_2–pentane to give 30 mg (0.085 mmol, 85%) of white, crystalline **13**: mp >200 °C dec; (CH_2Cl_2) 1770, 1720 cm^{-1}; mass spectrum exact mass calcd, m/e 347.155; found, m/e 347.157.

7-Diazocephalosporanic Acid *tert*-Butyl Ester (5). 7-Aminocephalosporanic acid *tert*-butyl ester (**4**,[2b] 164 mg, 0.5 mmol) was diazotized in a mixture of 50 ml of CH_2Cl_2 and 50 ml of ice water with 1.5 g of sodium nitrite and 95 mg of p-TSA–H_2O. After 5 min a total amount of 138 mg (0.77 mmol) of p-TSA–H_2O was added over a period of 37 min and stirring was continued for 3 min. The same work-up procedure as described for the synthesis of **3** was followed. Compound **5** (128–141 mg, 64–83%)[21] was isolated as a yellow solid, which was crystallized from CH_2Cl_2–petroleum ether (40:60): mp 99–99.5 °C dec; ir (CH_2Cl_2) 2180, 1765, 1730, 1710, 1635 cm^{-1}; NMR ($CDCl_3$) δ 5.5 (s, C_6 H), 4.83 (AB q, J = 18 Hz, C_2 CH_2), 2.03 (s, CH_3), 1.52 (s, t-Bu). Anal. Calcd for $C_{14}H_{17}N_3O_5S$: C, 49.54; H, 5.05; N, 12.38; S, 9.45. Found C, 49.98; H, 5.12; N, 12.28; S, 9.33.

Tri(4-benzoyloxybutyl)borane (16). To a solution of 422 mg (2.46 mmol) of 3-butenyl benzoate in 4 ml of dry THF was added 4.85 ml (0.85 mmol) of diborane in THF at a temperature of −10 °C. After stirring for 1 h at −10 °C and 30 min at room temperature, the excess of diborane was destroyed with 0.03 ml of water. This solution was used as such for the synthesis of **17**.

7-(4-Benzoyloxybutyl)cephalosporanic Acid *tert*-Butyl Ester (17). The procedure for the synthesis of **6** was followed, except that a solution of **5** was alkylated with borane **16**. Compound **17** was isolated as a colorless oil in 85% yield by preparative silica gel thin layer chromatography with CH_2Cl_2–10% ether as eluent. Despite extensive efforts, **17** could not be obtained in analytically pure form: ir (CH_2Cl_2) 3100, 1770, 1700–1740, 1640, 1600, 1580 cm^{-1}; NMR ($CDCl_3$) δ 7.9–7.4 (aromatic protons), 4.8 (AB q, J = 12 Hz, C_3 CH_2), ~4.55 (d, J = 5 Hz, C_6 H), 4.35 (d, J = 2.5 Hz, C_6 H), 4.25 (~t, $-CH_2O$), 3.32 (AB q, J = 18 Hz, C_2 CH_2), 2.0 (s, CH_3), 1.55–1.9 (m, 6 H), 1.5 (s, t-Bu), ~3.6 (m, C_7H), ~3.1 (m, C_7 H); mass spectrum m/e 433 (M^+ − 56), 374, 155, 115, 78, 71, 57; uv λ_{max} (95% EtOH) 265 nm (ϵ 7100), 228 (14 000).

Sodium 7-(4-Benzoyloxybutyl)cephalosporanate (18). The same procedure as for the preparation of **9** was followed. From 100 mg (0.20 mmol) of ester **17**, 90 mg of 7-(4-benzoyloxybutyl)cephalosporanic acid was isolated as an amorphous solid: ir (CH_2Cl_2) 3300–2500, 1775, 1730, 1700, 1600, 1580, 1560 cm^{-1}; NMR ($CDCl_3$) δ 7.9–7.4 (aromatic protons), 4.85 (AB q, J = 12 Hz, C_3 CH_2), ~4.55 (d, J = 5 Hz, C_6H), ~4.32 (d, J = 2.5 Hz, C_6 H), 4.25 (t, $-CH_2O$), 3.3 (AB q, J = 18 Hz, C_2 CH_2), 2.0 (s, CH_3), 1.5–2.0 (m, 6 H). Estimation of the exact mass was not possible, because the molecular ion peak was lacking in the mass spectrum. Purification was effected by converting the acid into the sodium salt **18**. The latter was isolated in 85% yield by lyophilization of an aqueous solution of pH 7.5: mp 150 °C dec; uv λ_{max} (H_2O) 230, 260 nm; ir (Nujol) 1770, 1730, 1649–1600, 1580 cm^{-1}.

Registry No.—**1**, 5299-66-1; **2**, 58249-90-4; **3**, 58249-91-5; **4**, 6187-87-7; **5**, 58249-92-6; **6**, 58249-93-7; **7**, 58249-94-8; **8**, 58249-95-9; **9**, 58249-96-0; **10**, 58249-97-1; **11**, 58249-98-2; **12**, 58249-99-3; **13**, 58250-00-3; **14**, 58250-01-4; **15**, 18203-32-2; **16**, 58250-02-5; **17**, 58250-03-6; **18**, 58250-04-7; 1-glycylpiperidine, 5649-08-1; 1-(*N*-benzyloxycarbonylglycyl)piperidine, 3886-37-1; 1-(α-diazoacetyl)-piperidine, 24761-87-3; trioctylborane, 3248-78-0; 7-aminodeacetoxycephalosporanic acid *tert*-butyl ester, 33610-06-9; triethylborane, 97-94-9; 7-(4-benzoyloxybutyl)cephalosporanic acid, 58250-05-8.

References and Notes

(1) (a) E. H. Flynn, "Cephalosporins and Penicillins", Academic Press, New York, N.Y., 1972; (b) *ibid.*, pp 96–105, for details about diazotation of 6-ADA, 7-ACA, and 7-ADCA and the preparation of 7-*epi*-chlorodeacetoxycephalosporanic acid.

(2) (a) T. Yen, J. Frazee, and J. R. E. Hoover, *J. Org. Chem.*, **38**, 2857 (1973); (b) E. H. W. Bohme, H. E. Applegate, J. B. Ensing, P. T. Funke,

M. S. Puar, and J. E. Dolfini, *J. Org. Chem.*, **38**, 230 (1973); (c) L. D. Cama and B. G. Christensen, *Tetrahedron Lett.*, 3505 (1973); (d) H. E. Applegate, J. E. Dolfini, M. S. Puar, W. A. Husarchyk, B. Toeplitz, and J. Z. Gougatas, *J. Org. Chem.*, **39**, 2794 (1974); (e) G. A. Koppel and R. E. Koehler, *J. Am. Chem. Soc.*, **95**, 2403 (1973); (f) H. Yanagiswa, M. Fukusima, A. Ando, and H. Wakao, *Tetrahedron Lett.*, 2705 (1975).

(3) Recently the synthesis of 7-β-phenoxyacetylpenicillanic acid was reported, which showed some antibiotic activity: J. C. Sheehan and Y. S. Lo, *J. Org. Chem.*, **38**, 3227 (1973).

(4) G. L. Biagi, M. C. Guerra, A. M. Barbaro, and M. F. Gamba, *J. Med. Chem.*, **13**, 511 (1970).

(5) J. Hooz and S. Linke, *J. Am. Chem. Soc.*, **90**, 6891 (1968). We have no ready explanation for the role which water plays in this reaction, since the reaction proceeds well under anhydrous condition on substrates used by Hooz. The presence of sulfur and the formation of the sulfoxide (**8**) need to be considered in this respect.

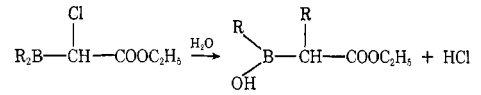
(6) Hydroboration of terminal simple alkenes gives rise to 6% addition of the boron to the 2 and 94% addition to the 1 position.[7] However, we could not detect any 1-(α-methylnonanoyl)piperidine using GLC and NMR techniques.

(7) H. C. Brown, "Boranes in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1972, Part 5.

(8) The synthesis of benzhydryl 7-diazocephalosporanate has been reported via diazotation of the amine. However, no yield and experimental details were given: L. D. Cama, R. J. Leanza, T. R. Beattie, and B. G. Christensen, *J. Am. Chem. Soc.*, **94**, 1408 (1972).

(9) H. C. Brown, M. H. Midland, and A. B. Levy, *J. Am. Chem. Soc.*, **94**, 3662 (1972).

(10) Nucleophilic induced substitution of the chloro substituent, occurring in more simple systems, is apparently not the case here (ref 9).



(11) H. C. Brown and M. K. Unni, *J. Am. Chem. Soc.*, **90**, 2902 (1968).

(12) H. C. Brown and R. L. Sharp, *J. Am. Chem. Soc.*, **90**, 2915 (1968).

(13) H. C. Brown and R. M. Gallivan, Jr., *J. Am. Chem. Soc.*, **90**, 2906 (1968).

(14) The two alcohols *N*-(4-hydroxybutyl)benzamide and *N*-(3-hydroxybutyl)-benzamide were formed in the ratio 89:11, which implied that 11% of the boron had been added to the 2 position of the alkene moiety of **19**.

(15) D. J. Pasto and P. W. Wojtkowski, *Tetrahedron Lett.*, 215 (1970).

(16) R. A. Firestone, N. S. Maciejewicz, R. W. Ratcliffe, and B. G. Christensen, *J. Org. Chem.*, **39**, 437 (1974).

(17) D. A. Johnson and D. Mania, *Tetrahedron Lett.*, 267 (1969).

(18) R. A. Firestone, N. Schelechow, D. H. R. Johnston, and B. G. Christensen, *Tetrahedron Lett.*, 375 (1972).

(19) D. M. Brunwin, G. Love, and J. Parker, *J. Chem. Soc. C*, 3756 (1971).

(20) H. C. Brown and G. Zweifel, *Org. React.*, **13**, 1 (1963).

(21) The yield of **5** strongly depends on the purity of the precursor **4** and the rate of addition of the *p*-toluenesulfinic acid to **4**.

Nitrosation of 1-Substituted Aziridines

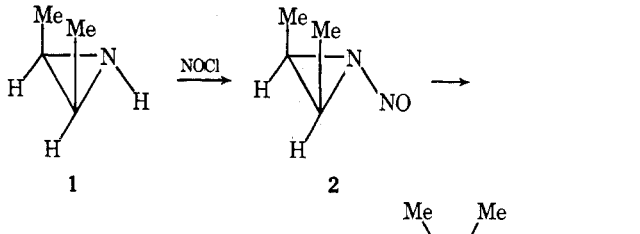
Richard N. Loeppky* and David H. Smith

Department of Chemistry, University of Missouri, Columbia, Columbia, Missouri 65201

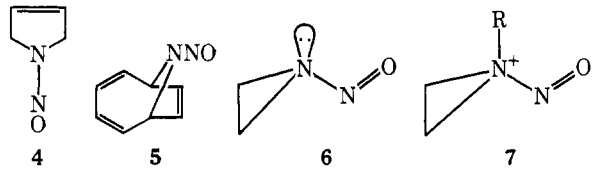
Received May 1, 1975

Three aziridines, (*Z*)-1-butyl-, (*Z*)-1-benzyl-, and (*Z*)-1-(4-chlorophenyl)-2,3-diphenylaziridine, have been prepared and their reaction with nitrous acid in acetic acid studied. The principal product of the *N*-alkylaziridine nitrosation has been assigned the structure of an *N*-alkylnitrosenamine, a new type of compound, on the basis of its chemical and spectroscopic behavior (including high-resolution MS and ^1H and ^{13}C NMR). Acid-catalyzed hydrolysis of (*E*)-1,2-diphenyl-1-(*N*-butyl)nitrosaminoethene gave benzoin in addition to the expected benzyl phenyl ketone. Other products from the nitrosation were benzaldehyde and *threo*-1,2-diphenyl-2-(*N*-butyl)nitrosaminoethyl acetate. The reaction of the *N*-arylaziridine with nitrous acid gave these latter two types of products, and *N*-4-chlorophenylbenzamide among others. Mechanisms which accommodate these findings are discussed.

Since the discovery of the facile nitrous oxide extrusion reaction of *N*-nitroso aziridines[1] this transformation (eq 1)



has been of considerable synthetic and theoretical interest.[2-7] Woodward and Hoffmann presented the reaction as an example of a nonlinear cheletropic cycloreversion in explaining the observation of both facile extrusion and retention of stereochemistry.[8] In principle two modes of decomposition are open to the *N*-nitroso aziridines, a linear conrotatory process and the observed disrotatory transformation, although geometric factors allow only this latter mode of decomposition. In order to explain the stability of *N*-nitroso-3-pyrroline **4** and the nitrous oxide adduct of cyclooctatetraene **5** Mock and Isaac[9] have postulated that unlike other nitrosamines the amino nitrogen of *N*-nitroso aziridine exists in a tetrahedral array **6** which uniquely predisposes it to cheletropic fragmentation. Examination of the correlation diagram of Mock and Isaac has led us to consider the fate of the related species **7** where the unshared pair is coordinated with an alkyl or aryl cation. It appears that such a species is capable of facile decomposition to an olefin and [R—N⋯N⋯O$^+$]. A species akin to **7**, the trialkylnitrosammonium ion **8**, has been shown by Smith and Loeppky[10] to lie on the pathway for the nitrosative cleavage of alkyl tertiary amines. This reaction, which has been periodically rediscovered over the past 100 years,[11] proceeds by the mechanism depicted in Scheme I. In this paper we



Scheme I