treatment of **1** in benzene at 80 °C gave thiolactam **2**[8] (mp 151–152 °C), which was converted to the vinylogous carbamate **3**[8] (mp 177–178 °C; λ_{max}^{MeOH} 283 nm (ϵ 19 900); $\delta_{ppm}^{CDCl_3}$ 1.60 (2 H, m), 2.34 (2 H, t, J = 7 Hz), 3.52 (2 H, t, J = 7 Hz), 3.62 (3 H, s), 4.00 (4 H, m), 4.90 (1 H, s), 7.58 (1 H, broad s)) in two steps (1. $CH_3COCHBrCO_2CH_3$/$NaHCO_3$/CH_2Cl_2/reflux,[9] 2. KOH/CH_3OH/50 °C) in 50% overall yield from **1.** The vinylogous carbamate **3** was condensed with benzyloxyacetaldehyde[10] and silicon tetraisothiocyanate[11] in benzene at room temperature, followed by a 110 °C workup in toluene,[12] to yield the thiourea ester **4**[8] (mp 147–148 °C; λ_{max}^{MeOH} 310 nm (ϵ 11 700); $\delta_{ppm}^{CDCl_3}$ 1.40 (2 H, m), 2.33 (2 H, m), 3.47 (2 H, m), 3.75 (3 H, s), 3.95 (6 H, m), 4.40 (1 H, m), 4.50 (2 H, s), 6.87 (1 H, broad s), 7.26 (5 H, s)) in 75% yield. The structure of **4** was concluded from the fact that **4** could be smoothly converted in two steps (1. $Et_3O^+BF_4^-$/$NaHCO_3$/CH_2Cl_2/room temperature, 2. *m*-$ClC_6H_4CO_3H$/wet CH_2Cl_2/0 °C) to the 2-oxo-dihydropyrimidine **5**[8] (mp 134–135 °C; λ_{max}^{MeOH} 293 nm (ϵ 7400)), which was identical with the authentic substance prepared by the isocyanic acid procedure reported previously.[13] The thiourea ester **4** was transformed to the thiourea urea **6**[8] (mp 124–126 °C; λ_{max}^{MeOH} 262 nm (ϵ 8600), 307 (9900); $\delta_{ppm}^{CD_3OD}$ 1.45 (2 H, m), 2.15 (1 H, m), 2.65 (1 H, m), 3.52 (2 H, d, J = 4 Hz), 3.73 (2 H, d, d, J = 9, 6 Hz), 4.00 (4 H, m), 4.54 (2 H, s), 5.02 (1 H, t, J = 4 Hz), 7.26 (5 H, s)) in four steps (1. $NH_2NH_2{\cdot}H_2O$/CH_3OH/room temperature, 2. NOCl/CH_2Cl_2/−50 °C, 3. 90 °C/C_6H_6, 4. NH_3/C_6H_6/room temperature) in 75% overall yield.

The cyclization condition previously developed in this laboratory[13] was not suitable for the thiourea urea **6,** since **6** was extremely acid labile. This difficulty was overcome by exchanging the ketal group of **6** with the thioketal group (note acid stability of thioketals). Thus, **6** was converted into the thioketal thiourea **7**[8] (mp 108–111 °C; λ_{max}^{MeOH} 265 nm (ϵ 9200), 301 (8900); $\delta_{ppm}^{CDCl_3}$ 2.00 (2 H, m), 2.80 (6 H, m), 3.57 (2 H, m), 4.01 (2 H, m), 4.54 (2 H, s), 4.75 (2 H, broad s), 4.85 (1 H, m), 6.68 (1 H, broad s), 6.75 (1 H, broad s), 7.28 (5 H, s)) in 63% yield by treatment with 1,3-propanedithiol in acetonitrile in the presence of boron trifluoride etherate at room temperature. The thioketal thiourea **7** was warmed in a mixture of acetic acid and trifluoroacetic acid (v/v = 9/1) at 50 °C for 18 h to yield the tricyclic thiourea **8**[8] (50% yield; mp 158–160 °C; λ_{max}^{MeOH} 255 nm (ϵ 20 400); $\delta_{ppm}^{CD_3OD}$ 1.95 (2 H, m), 2.30–3.10 (6 H, m), 3.40–4.15 (5 H, m), 4.54 (2 H, s), 4.63 (1 H, d, J = 2 Hz), 7.31 (5 H, s)) and its C_6 epimer **9**[8] (10% yield; mp >325 °C; λ_{max}^{MeOH} 255 nm (ϵ 20 300); $\delta_{ppm}^{Me_2SO\text{-}d_6}$ 1.85 (2 H, m), 2.75–3.10 (6 H, m), 3.15–3.95 (6 H, m), 4.47 (2 H, s), 6.92 (1 H, s), 7.30 (5 H, s), 7.70 (1 H, s), 8.04 (1 H, s)).[13,14] In neat trifluoroacetic acid,[13] the ratio of the cyclization products **8** and **9** was 1:5 in favor of **9.** The tricyclic thioureas **8** and **9** were not interconvertible under acetic acid–TFA or –TFA conditions. A possible rationalization for the stereochemistry outcome of this cyclization had been proposed.[13] The stereochemistry assignment of **8** was made by analysis of the NMR spectrum; $J_{5,6}$ was found to be 2.0 Hz for **8,** which is close to that (1.3 Hz) of saxitoxin.[15]

The tricyclic thiourea **8** was converted to the diguanidine **10** in two steps (1. $Et_3O^+BF_4^-$/$NaHCO_3$/CH_2Cl_2/room temperature, 2. $EtCO_2NH_4$/135 °C). The product was isolated as its dipicrate salt[8] (mp 124–126 °C; $\delta_{ppm}^{CD_3OD}$ 2.04 (2 H, m), 2.3–3.2 (6 H, m), 3.63 (5 H, m), 4.51 (2 H, s), 4.95 (1 H, d, J = 1 Hz), 7.25 (5 H, s), 8.71 (4 H, s)) in 33% yield.[16] The hydrochloride salt of **10** was treated with boron trichloride in methylene chloride at 0 °C to yield decarbamoylsaxitoxin thioketal **11,** which was isolated as its hexaacetate[8] (Ac_2O/Py/room temperature) in 75% yield. NBS treatment of the hexaacetate in wet acetonitrile at 15 °C, followed by methanol treatment at 100 °C, gave decarbamoylsaxitoxin **12**[8] dihydrochloride as an amorphous solid (homogeneous on silica gel TLC in different solvents systems[17]) in 30% yield.[18] Decarbamoylsaxitoxin thus synthesized was identical with the authentic decarbamoylsaxitoxin, derived from natural saxitoxin,[17,19] by comparison of the NMR spectrum, silica gel TLC in different solvent systems,[17] and toxicity.

Chlorosulfonyl isocyanate[20] treatment of **12** in formic acid at 5 °C, followed by hot water workup, gave *d,l*-saxitoxin **13**[8] sulfate. The synthetic substance was isolated by workup with a weakly acidic ion exchange resin and then Sephadex LH-20 column chromatography in 50% yield.[18,21] Synthetic saxitoxin was an amorphous solid (homogeneous on silica gel TLC in different solvent systems[2]) and identical with natural saxitoxin[19] by comparison of the NMR spectrum, silica gel TLC, and toxicity.[22]

Acknowledgment. Financial assistance from National Institutes of Health, Milton Fund, Hoffmann-La Roche Company, and Astra Pharmaceutical Products is gratefully acknowledged.

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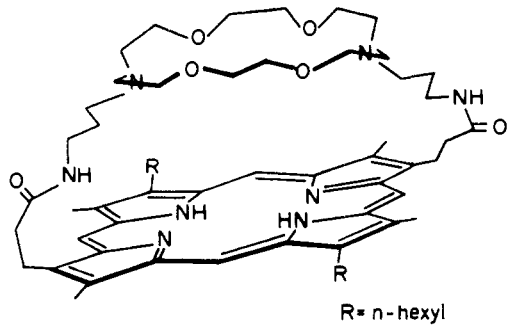
H. Tanino, T. Nakata, T. Kaneko, Y. Kishi*
Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138
Received December 8, 1976

Stacked Double-Macrocyclic Ligands. 1. Synthesis of a "Crowned" Porphyrin

Sir:

The recognition that a large number of enzymes have two metal ions held in close proximity in their active sites has stimulated considerable interest in the chemistry of binuclear

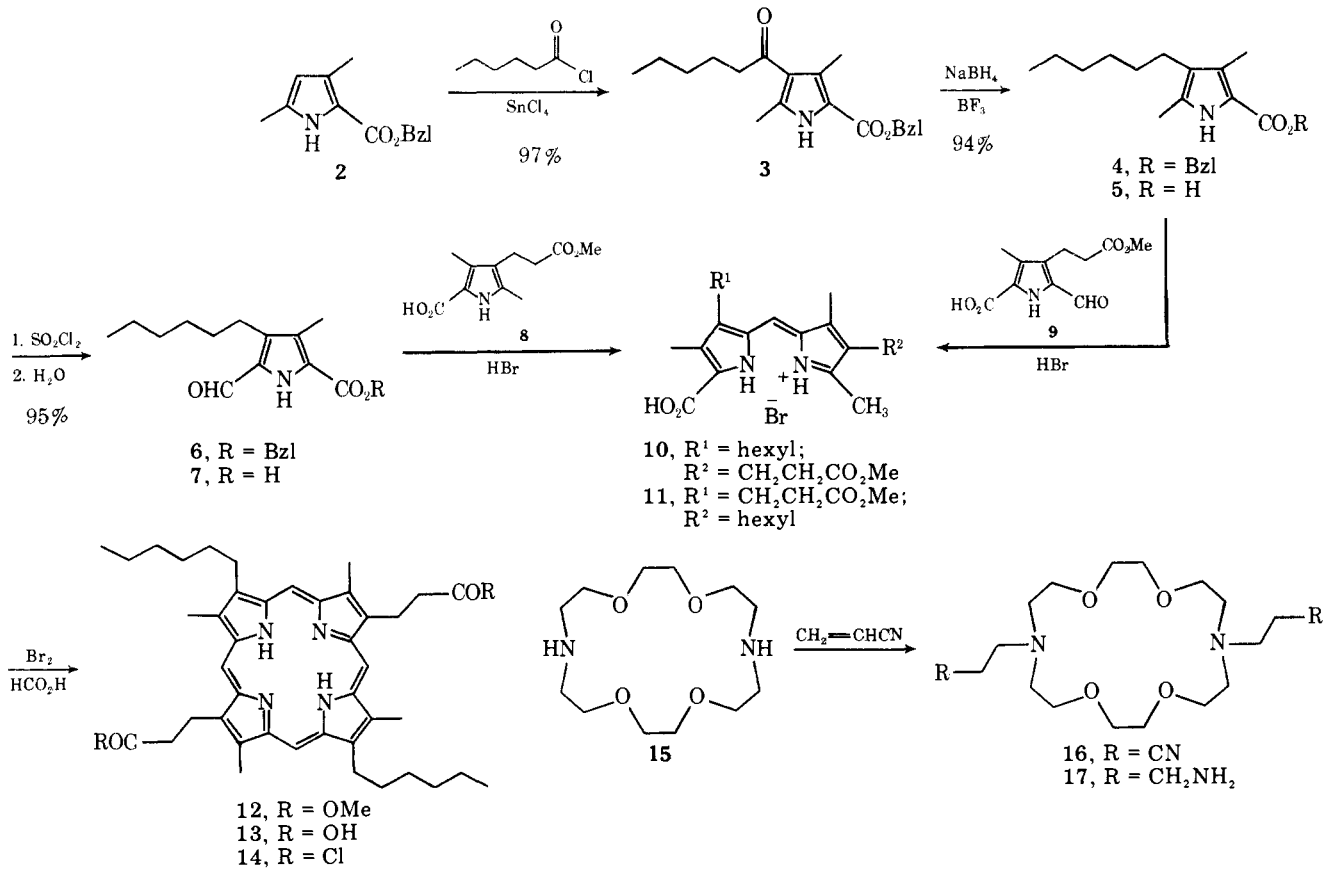


CROWNED PORPHYRIN
1

metal complexes.[1,2] A binuclear metal ligand capable of constraining two metal ions at strategic positions could be an attractive model for the metalloproteins. The author wishes to report the synthesis of a novel dimetal ligand, designated as the "crowned" porphyrin (**1**), that has the ability to accommodate a transition metal ion and a group 1A or group 2A cation simultaneously.

Strategically, the synthesis of a crowned prophyrin is similar to the synthesis of porphyrins with protective structures covering one face of the porphyrin plane. Two approaches have been developed. One route begins with the nonporphyrin part and porphyrin precursors are built onto the two ends of this structure. The porphyrin ring is finally cyclized by intramolecular condensation. Examples of this route include the original "cyclophane porphyrin"[3] and the "capped"[4] and the "strapped" porphyrins.[5] An alternative bridge-forming method starts with the porphyrin nucleus.[6,7] Functional groups are introduced to the two diagonally substituted side chains and the two chains can then be condensed with another bifunctional molecule to form the bridge. The latter method may not be as synthetically intriguing as the former approach, but clearly would be more widely applicable. The only drawback is that symmetrically functionalized porphyrins cannot be obtained by modifying the naturally occurring type IX porphyrins[8] and have to be synthesized from pyrrole precursors, which can be prohibitively lengthy and laborious. The author reports here an extremely simple and efficient route to the preparation of type II substituted deuteroporphyrins (e.g., porphyrins with a substitution pattern of **12**).

Dihexyldeuteroporphyrin II (**13**) was chosen for elaboration mainly because of its extremely high solubility in organic solvents, which is essential for successful separation and purification of the final polycyclic porphyrin products. The hexyl side chains were introduced to pyrrole components by acylation of benzyl 2,4-dimethylpyrrole-5-carboxylate (**2**)[9] in the presence of $SnCl_4$,[10] followed by diborane reduction[11] of the resulting β-carbonylpyrrole **3.** The 2-methyl group of **4** was dichlorinated with SO_2Cl_2 at high dilution;[12] the reaction mixture was then stirred with H_2O overnight to afford the pyrrole aldehyde **6** in 95% yield. After catalytic debenzylation, the free acid **7** was mixed with equimolar pyrrole acid **8**[13] in an acetonitrile–methanol (1:1) mixture and treated with 48% HBr at refluxing temperature. Formation of the dipyrromethene **10** was instantaneous. After the solvent was removed, the crude dipyrromethene was self-condensed in hot formic acid with excess bromine to give **13.** This one-pot porphyrin synthesis afforded a 16–20% yield from the aldehyde **7.** Alternatively, porphyrin **13** can be obtained in equally good yield by condensation of pyrrole **5** and aldehyde **9**[12] via the isomeric dipyrromethene **11** intermediate. This procedure avoided the erratic preparation of 5-bromo-5′-methyl- or 5-bromo-5′-bromomethyldipyrromethene intermediates as required in the traditional Fischer's method[14] and escalated the multistep procedure involving the perbromide intermediate as recommended by Smith.[15] Since the pyrrole precursors can be easily synthesized in kilogram quantities, supply of the porphyrin is virtually unlimited. The porphyrin dimethyl ester **12** was



2

3

4, R = Bzl
5, R = H

6, R = Bzl
7, R = H

8

9

10, R^1 = hexyl; R^2 = $CH_2CH_2CO_2Me$
11, R^1 = $CH_2CH_2CO_2Me$; R^2 = hexyl

12, R = OMe
13, R = OH
14, R = Cl

15

16, R = CN
17, R = CH_2NH_2

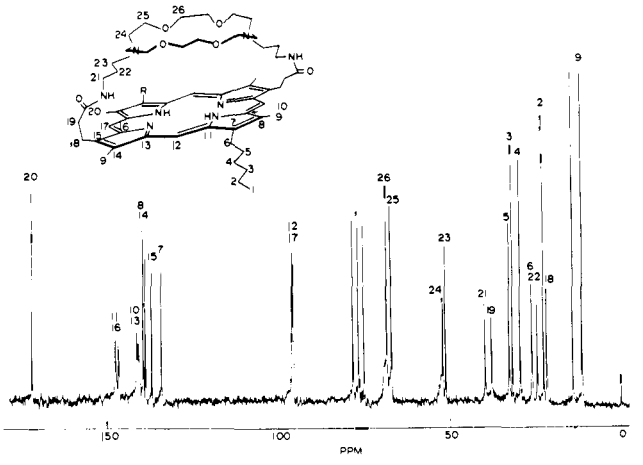


Figure 1. ^{13}C NMR spectrum of **1** ($CDCl_3$). Chemical shifts of the porphyrin **1** are found almost identical with those of the parent porphyrin **12**, except that the carbonyl peak has shifted 1.5 ppm upfield. The six carbon signals of the aza-crown ether are within 3 ppm from the parent compound **17**.

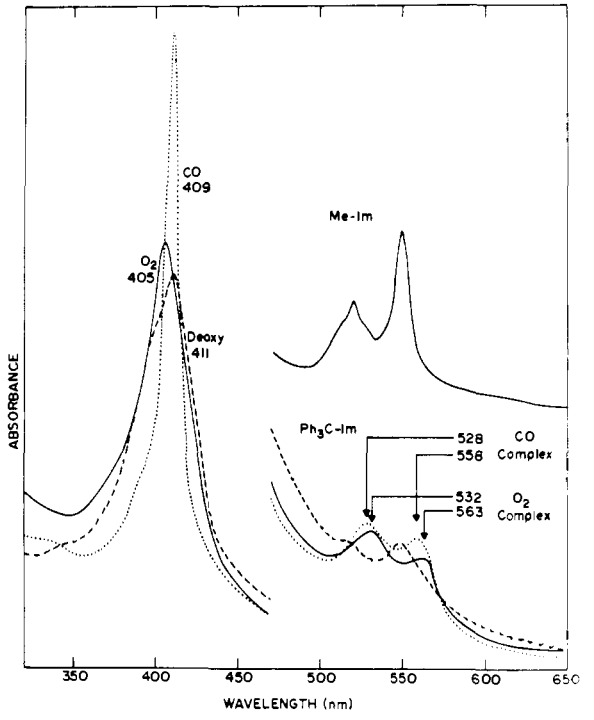


Figure 2. Absorption spectra of O_2 and CO adducts of the Fe(II) porphyrin **1** and 1-triphenylmethylimidazole complex in DMA at 24 °C: (---) deoxy spectrum, under argon; (—) under 1 atm of O_2; (···) spectrum recorded after the O_2 atmosphere was replaced by CO. CO can be photolyzed off to give the deoxy species and the cycle can be repeated at 24 °C without appreciable oxidation. The trace at upper-right corner is the deoxy spectrum of the Fe(II) porphyrin **1** and 1-methylimidazole complex. In these experiments, [heme] = 1×10^{-5} M, [Ph_3C-Im] or [Me-Im] = 1×10^{-2} M.

crystallized in huge needles from $CHCl_3$–MeOH mixtures. (Anal. Calcd for C, H, N: C, 74.79; H, 8.22; N, 7.93. Found: C, 74.60; H, 8.34, N, 7.99: M^+ 706).

The crown ether component was synthesized from diaza-18-crown-6, **15** (Kryptofix 2,2).[16] The cyanoethyl side chains were introduced by refluxing **15** in acrylonitrile for 72 h (**16**, mp 49 °C). Hydrogenation of **16** in ammonia saturated methanol with Raney Ni afforded the bisaminopropyl derivative **17**, with almost quantitative yield from **15**.

The coupling of the two ligands was effected under high dilution conditions. The porphyrin diacid chloride **14** (obtained by treating **13** with oxalyl chloride) and the bisamino crown ether **17** (1.5 molar equiv) in CH_2Cl_2 were injected simultaneously to a refluxing benzene–CH_2Cl_2 (1:1) mixture via a syringe pump over a period of 4 h. Being the only movable product on thin layer silica gel plates ($CHCl_3$), the crowned porphyrin **1** can be easily isolated in 65% yield. Proton magnetic resonance spectral ($CDCl_3$) data were in complete accord with the indicated structure. The two amide protons were at δ 5.91. The methylene protons of the crown ether were found in groups at δ 0.6, 1.4, and 1.8, shifted approximately δ 1.5 upfield from their normal signals by the diamagnetic ring current of the suspended porphyrin. Carbon-13 NMR showed 26 well-resolved signals (Figure 1) but the anisotropic shifts were much less pronounced. The mass spectral parent ion with the expected atomic mass units (1018) has been obtained.

The size of the cavity between the porphyrin and the crown ether has been probed by ligand binding to the Fe (II) complex.[17] In the presence of 1-methylimidazole or 1-isobutylimidazole,[18] the Fe(II) complex exhibits a regular six-coordinate hemochrome spectrum (α 548 nm > β 529 nm, S 413 nm). These complexes bind O_2 at room temperature with a half-life about 3 min, indicating that O_2 molecules as well as the imidazole ligands are able to enter the cavity.[19] With a larger ligand such as 1-triphenylmethylimidazole,[18] the visible spectrum is distinctively different from the hemochrome (Figure 2) and the oxygenated species is found stable at 25 °C ($t_{1/2}$ > 1 h), indicating that the N-base is coordinate only at the free side with the O_2 encumbered under the "crown" to escape from bimolecular oxidation.[20] Therefore, the distance of the gap is probably close to 6 Å.[21] Further studies of the effect of cations on heme-O_2 complexes as well as the synthesis of other dimetal complexes are underway. Preliminary ^{23}Na and ^{133}Cs NMR data indicate that complexation of these cations by **1** is indeed effective.

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(19) Simple hemes under similar conditions would only give incomplete oxygenation and are oxidized totally in less than 30 s. The enhanced O_2 binding ability and stability of the "crowned" heme implies a weaker than normal bonding between the iron and the imidazole under the "crown", presumably for steric reasons.
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(21) Estimated with the aid of CPK models.

C. K. Chang
Department of Chemistry, Michigan State University
East Lansing, Michigan 48824
Received January 17, 1977

The Conversion of 3-*exo*-Methylenecephalosporin to 3-Halomethylcephems; a Convenient Synthesis of 3′-Substituted Cephalosporins from Penicillins

Sir:

Recently, Kukolja and co-workers reported a novel conversion of penicillin sulfoxide (**1**) to 3-*exo*-methylenecephem sulfoxide (**2**).[1] The unusual functionality at C_3 (i.e., exo-olefin) presented a potential route to 3-halomethylcephems (**3** → **5**).

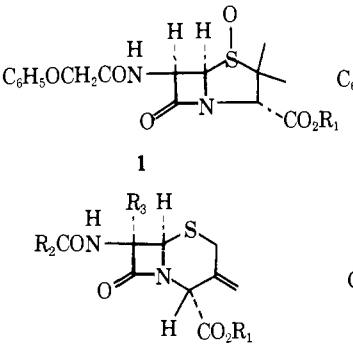
Surprisingly, the 3-*exo*-methylene olefin does not add halogens under usual conditions.[2] We have found, however, a new method to convert the 3-*exo*-methylenecephems to the 3-halomethyl system. This process depends on the activation of the 3-*exo*-methylene by conversion to an allylic anion, A. This anion is subsequently trapped with an electrophile to give a halomethylcephem, **5**.[3]

The observation that led us to this new process was that treatment of **3a** with lithium methoxide and 2 equiv of *tert*-butyl hypochlorite in tetrahydrofuran (THF) at 80 °C afforded **5a** in 40% yield: IR ($CHCl_3$) 1786, 1745, 1705 cm^{-1}; NMR ($CDCl_3$) δ 3.38 (bs, 2, C_2-H), 3.46 (s, 3, C_7-OCH_3), 3.82 (s, 2, side chain CH_2), 4.34 (s, 2, C_3-CH_2Cl), 5.04 (s, 1, C_6-H), and 6.8–7.6 (ArH).[4,5]

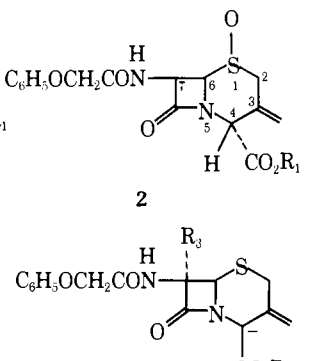
This reaction of the usually inert 3-*exo*-methylene functionality can be explained if we presume that the double bond was activated by conversion to the allylic anion, A (R_3 = H or OCH_3), which was subsequently intercepted with chlorine at the γ-carbon.[6] We theorized that if a base-electrophile combination could be found that would be specific for the C_4 hydrogen-C_3-*exo*-methylene, then a conversion of the 3-*exo*-methylene to the 3-halomethylcephem could be carried out without concomitant oxidation at C_7. When cephem **3b** was treated with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) and bromine in tetrahydrofuran over a temperature range of −80 to 0 °C, there was obtained upon workup **5b** in 80% yield: IR ($CHCl_3$) 1785, 1745, 1705 cm^{-1}; NMR ($CDCl_3$) δ 3.6 (bs, 2, C_2-H), 4.46 (bs, 2, C_3-CH_2Br), 4.58 (s, 2, side chain CH_2), 5.05 (d, 1, J = 5 Hz, C_6-H), 5.40 (s, 2, ester CH_2), 5.95 (q, 1, J = 5 and 9 Hz, C_7-H), and 6.8–8.3 (ArH).[7]

This reaction obviously supports our suppositions. Further support was obtained from modifications of this reaction.

When cephem **3a** was treated as above with DBU–bromine followed by quenching with trimethyl phosphite at 0 °C, there was obtained upon workup **5c** in 63% yield: IR ($CHCl_3$) 1785, 1745, 1705 cm^{-1}; NMR ($CDCl_3$) δ 3.50 (bs, 2, C_2-H), 3.84 (s, 2, side chain CH_2), 4.30 (s, 2, C_3-CH_2Br), 4.98 (d, 1, J = 4.5 Hz, C_6-H), 5.86 (q, 1, J = 4.5 and 9 Hz, C_7-H), 6.84 (d, 1, J = 9 Hz, side chain NH), and 7.0–7.6 (ArH).[8]

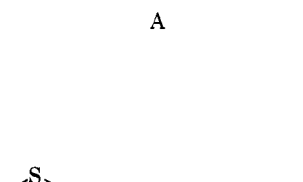


1

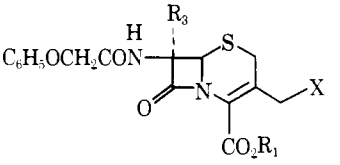


2

3a, R_1 = benzhydryl
R_2 = 2-thienylmethyl
R_3 = H
b, R_1 = *p*-nitrobenzyl
R_2 = phenoxymethyl
R_3 = H



A



5a, R_1 = benzhydryl; R_2 = thienyl methyl; R_3 = OCH_3; X = Cl
b, R_1 = *p*-nitrobenzyl; R_2 = phenoxymethyl; R_3 = H; X = Br
c, R_1 = benzhydryl; R_2 = 2-thienylmethyl; R_3 = H; X = Br
d, R_1 = *p*-nitrobenzyl; R_2 = phenoxymethyl; R_3 = H; X = I
e, R_1 = *p*-nitrobenzyl; R_2 = phenoxymethyl; R_3 = H; X = OAc
f, R_1 = *p*-nitrobenzyl; R_2 = phenoxymethyl; R_3 = H; X = *N*-methylthiotetrazole

The general versatility of this method was further demonstrated by the reaction of cephem **3b** with DBU–I_2 in THF from −80 to 0 °C to give the 3-iodomethylcephem **5d**, IR ($CHCl_3$) 1785, 1745, 1703 cm^{-1}; NMR ($CDCl_3$) δ 3.44 and 3.82 (ABq, 2, J = 18 Hz, C_2-H), 4.40 (s, 2, C_3-CH_2I), 4.54 (s, 2, side chain CH_2), 4.98 (d, 1, J = 5 Hz, C_6-H), 5.34 (s, 2, ester CH_2), 5.82 (q, 1, J = 5 and 9 Hz, C_7-H), and 6.8–8.4 (ArH).[9]

Since we had the halomethylcephems in hand, we treated them with appropriate 3′-nucleophilic reagents to form 3′-substituted cephems. These reactions provide a conversion of penicillin to biologically important cephems. Treatment of **5b** with silver acetate in acetic acid afforded **5e** in 30% yield.[10] Similarly, the reaction of **5b** with 1.2 equiv of *N*-methylthiotetrazole in dimethylformamide afforded cephem **5f** in 97% yield: IR ($CHCl_3$) 1785, 1745, 1705 cm^{-1}; NMR ($CDCl_3$) δ 6.0 (d, 1, J = 5 Hz, C_7-H), 5.5 (s, 2, ester CH_2), 5.1 (d, 1, J = 5 Hz, C_6-H), 4.0 (s, 3 H, N-CH_3).[11]

These are examples of the utilization of the 3-*exo*-methylenecephem in the synthesis of biologically important cephems.

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References and Notes

(1) S. Kukolja, S. R. Lammert, M. R. Gleissner, and A. I. Ellis, *J. Am. Chem. Soc.*, **98**, 5040 (1976).
(2) We found the 3-*exo*-methylene olefin of both the cephem sulfoxide or the corresponding sulfide afforded starting material or decomposition products