1,1-dicyclopropylethylene, 822-93-5; *tert*-butylethylene, 558-37-2; cyclohexene, 110-83-8; cyclooctene, 931-88-4; norbornene, 498-66-8; vinyl acetate, 108-05-4; 2,2-dimethyl-3-(trimethylsiloxy)-3-butene, 17510-46-2; 1-phenyl-1-(trimethylsiloxy)ethylene, 13735-81-4; *p*-benzoquinone, 106-51-4; 2-(3-methyl-2-butenyl)-*p*-benzoquinone, 5594-02-5; 7-phenylbicyclo[4.2.0]-3-octene-2,5-dione, 70681-10-6; 2,6-dimethyl-*p*-benzoquinone, 527-61-7; 3',3'-diphenylspiro[2,5-cyclohexadien-1,1'-[2]oxacyclobutan]-4-one, 81741-26-6; (1'α,2'β,5'β,6'α)-spiro[2,5-cyclohexadiene-1,4'-[3]oxatricyclo[4.2.1.0^{2,5}]nonan]-4-one, 72283-21-7; 3-methyl-2-butenyl-*p*-benzoquinone, 81741-27-7; 2-methyl-3-(2-hydroxyethyl)-1,4-dimethoxynaphthalene, 51794-09-3; 2-methyl-3-(2-hydroxyethyl)-1,4-naphthoquinone, 76670-45-6; methyl lapachol, 17241-45-1.

Mild and Simple Biomimetic Conversion of Amines to Carbonyl Compounds

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Abstract: 4-Formyl-1-methylpyridinium benzenesulfonate is a convenient reagent for the chemical modification of primary amines to aldehydes and ketones. This method mimics the biological process for transamination reactions with pyridoxal (vitamin B_6). As in that process, it involves imine formation, prototropic rearrangement, and hydrolysis. The conditions are extremely mild and are compatible with a large variety of sensitive functional groups. This process provides a simple and efficient alternative to the somewhat harsher procedures generally employed for such transformations.

Methods for the preparation of aldehydes and ketones are of constant interest, as evidenced by the vast body of accumulated literature on this subject. Typically, oxidations of primary and secondary alcohols and controlled reduction of certain carboxylate moieties most commonly afford the desired carbonyl compounds. The transformation of primary amines to carbonyl compounds has also received considerable attention. A variety of metal oxidizing reagents have been used, including $KMnO_4$,[1] K_2FeO_4,[2] $Pb(OAc)_4$,[3] and NiO_2,[4] with varying results. The photolytic intermediacy of benzophenone[5] has also been investigated for the conversion of some simple primary amines to carbonyls. However, hydrolysis of the resulting imines affords a 50% yield of ketone, at best, necessitating the recovery of amine educt. The utility of chloramine intermediates[6] and dehydrogeneration with selenium reagents or via sulfinamides has also been demonstrated,[7] although formation of these imines and their hydrolysis often require elevated temperatures and strong acid.

A variety of transaminations have been developed that involve prototropic rearrangement and equilibration of Schiff-base intermediates to avoid these direct amine oxidations. The utility of the Sommelet reaction[8] suffers seriously from the hydrolytic conditions generally employed, and yields are frequently unacceptable for preparative purposes. Various nitroaryl aldehydes[9] have been used to study the position of Schiff-base equilibrium, and subsequent reactions afforded carbonyl compounds with generally poor results. Imines prepared from 3,5-di-*tert*-butyl-1,2-benzoquinone have been utilized[10] to afford ketones in high yield, although this method is not applicable to the preparation of aldehydes. Some complex heterocyclic systems[11,12] have been employed and in special cases are effective transaminating reagents. However, they involve multiple steps, and their utility has not been generally demonstrated.

One recent example of the prototropic rearrangement method involves the formation of imines with pyridine-2-carboxaldehyde.[13] Deprotonation with lithium diisopropylamide afforded the resonance-stabilized anion, which was subsequently protonated and hydrolyzed, affording some simple aldehydes and ketones in high yields. The chief disadvantage of this process lies in the strong base required and its potential incompatibility with functional groups in more complex substrates. Although this method was described as a biomimetic approach to the oxidative deamination of primary amines, a more precise modeling of the biological process might afford milder reaction conditions and therefore be compatible with a wide variety of functional groups.

The role of pyridoxal phosphate (**1**, vitamin B_6) in biological transamination sequences is well established.[14] This cofactor is exceptionally receptive to nucleophilic addition because of its highly polarized carbonyl group and therefore readily converts primary amines to their corresponding imines (Scheme I). The enzyme system responsible for the efficiency of this overall process serves two fundamental functions: (1) controlled protonation of the pyridine nitrogen and (2) subsequent abstraction of an imine hydrogen, initiating prototropic rearrangement of the original Schiff base. We projected that a quaternized pyridine-4-carboxaldehyde might suitably mimic the biological system when applied to the in vitro preparation of some functionalized aldehydes and ketones. Such a system has been developed and is presented in this report.

Results and Discussion

Our purpose was to develop a simple, mild, efficient, and versatile conversion of primary amines to aldehydes and ketones via a route that in principle mimics the pyridoxal–pyridoxamine (**1–2**, Scheme I) interconversion. In addition, we sought a convenient method for product isolation that would not require formation of related derivatives or chromatographic separations. The use of water-soluble pyridinium salts would thus afford clean separation of carbonyl products from all starting materials and intermediates. First, some simple transamination reactions were examined with 4-formyl-1-methylpyridinium iodide[15] (**3**). The

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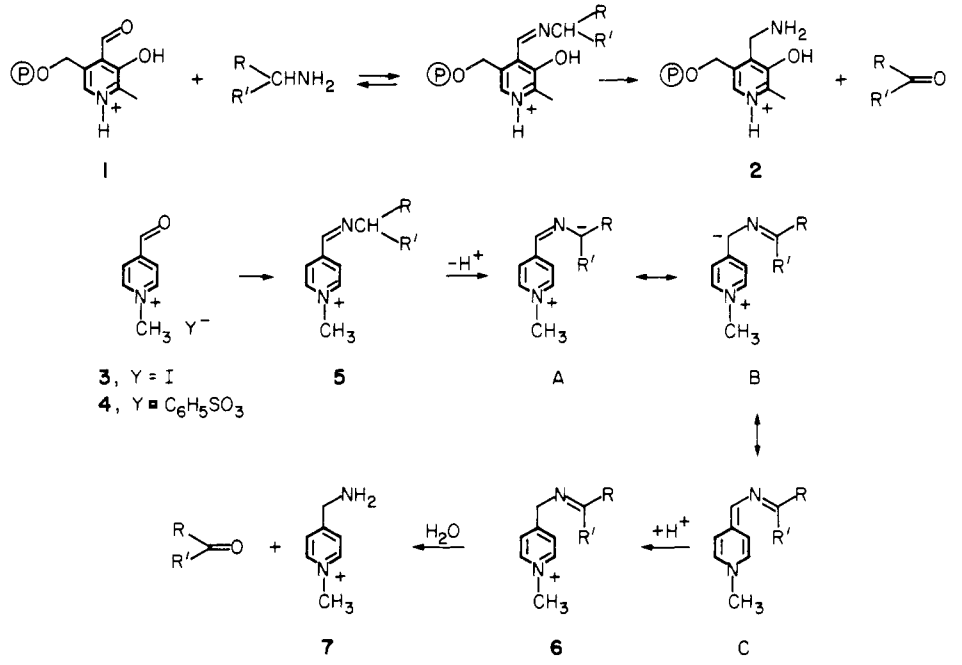
Scheme I. Transamination for 4-Formyl-1-methylpyridinium Salts as a Mimic of Pyridoxal



yields of valeraldehyde and cyclohexanone (from *n*-pentylamine and cyclohexylamine, respectively) varied considerably due to interference from iodide ion. This problem was solved by utilizing 4-formyl-1-methylpyridinium benzenesulfonate (**4**). Counterion oxidation–reduction interference was thus eliminated during the transamination process.

A general procedure was developed that allowed for convenient and efficient handling of all materials involved. Reactions were performed at room temperature in CH_2CL_2/DMF with a slight excess of the pyridinium salt. Consumption of amine was easily monitored by TLC (ninhydrin), and after a brief equilibration period followed by hydrolysis with aqueous oxalic acid, the pure carbonyl compound could be isolated by extraction. In this manner, nine primary amines were efficiently converted to their corresponding aldehydes or ketones, as shown in Table I.

Most reactions required DBU for efficient imine equilibration; however, the presence of electron-withdrawing substituents further facilitated proton abstraction (as in examples 3 and 5). The overall increase in Schiff-base acidity relative to pyridine-2-methylimino systems[13] must be attributed to the highly electron-withdrawing nature of the quaternized pyridine nitrogen. As a result, deprotonation occurs under relatively mild conditions, thus establishing imine equilibration. Uncharged resonance form C (Scheme I) contributes greatly to the overall stability of this important reaction intermediate. Subsequent reprotonation affords the desired imine **6**, which is then hydrolyzed to the 4-(aminomethyl)-1-methylpyridinium ion (**7**) and the carbonyl component.

The preparation of representative aldehydes and ketones by this method is straightforward. Phenylacetaldehyde, an often troublesome compound to prepare and isolate, is readily available from the corresponding β-phenylethylamine. It is probable that a wide variety of such arylacetaldehydes will be accessible by this route.

The transamination of *tert*-butyl 7-aminodeacetoxycephalosporanate (example 5) afforded the desired 7-oxo-β-lactam in good yield. However, instability necessitated immediate reduction to the corresponding α alcohol using $NaCNBH_3$. The corresponding ketone of 6-aminopenicillanic acid benzhydrol ester could not be isolated or reduced before total decomposition of the β-lactam moiety. However, the integrity of the cephalosporin ring system was maintained, illustrating the mild nature of this process.

1,3,4,6-Tetra-*O*-acetyl-α-D-glucosamine (example 6) afforded a mixture of anomeric acetates. Hydrolysis allowed pyranose ring opening, and depending upon the duration of hydrolysis, either an α,β-pyranose or α,β-furanose mixture of the triacetylglucosone could be cleanly isolated. The furanose products were always observed after longer hydrolytic periods and were also prepared from the pyranose mixture upon retreatment with aqueous oxalic acid. Exhaustive hydrolysis afforded a light yellow oil identical with an authentic sample of glucosone[16] that exists in a multitude of isomeric structures. In this regard, the 3,4,6-tri-*O*-acetylglucosone prepared above constitutes a relatively simple example of furanose and pyranose glucosone structures.

Table I. Oxidative Conversion of Primary Amines to the Corresponding Carbonyl Compounds with 4-Formyl-1-methylpyridinium Benzenesulfonate (**4**)

amine	base	product	% yield
1, *n*-pentylamine	DBU	pentanal	84
2, cyclohexylamine	DBU	cyclohexanone	91
3, α-phenylethylamine	Et_3N	acetophenone	94
4, β-phenylethylamine	DBU	phenylacetaldehyde	83
5, 7-aminodeacetoxy-cephalosporanic acid, *tert*-butyl ester	Et_3N	7-oxodeacetoxy-cephalosporanic acid *tert*-butyl ester	77[a]
6, 1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine	DBU	3,4,6-tri-*O*-acetyl-glucosone	85[b]
7, N^{α}-Cbz-lysine (**9**)	DBU	α-aminoadipic acid pipecolic acid	82 87
8, N^{α}-Cbz-lysine isopropyl ester (**23**)	DBU	α-aminoadipic acid pipecolic acid	81 89
9, N^{α}-ethoxycarbonyllysine isopropyl ester (**27**)	DBU	α-aminoadipic acid	92

[a] Isolated as the *tert*-butyl ester of 7-hydroxydeacetoxy-cephalosporanic acid. [b] Isolated as a mixture of furanose and pyranose forms.

Oxidation of the ε-amino group of lysine (**8**) was of particular interest (see Scheme II). Lysine is cheap and contains the six carbon atoms and α-asymmetry required for the preparation of α-aminoadipic and pipecolic acids if clean oxidation could be effected at the ε-amino group. Our interest in these conversions stemmed from the fact that neither amino acid is readily available in optically pure form and both are useful synthetic intermediates.

Various preparations of optically active α-aminoadipic acid have been reported utilizing glutamic acid,[17] ω-bromobutyronitrile,[18]

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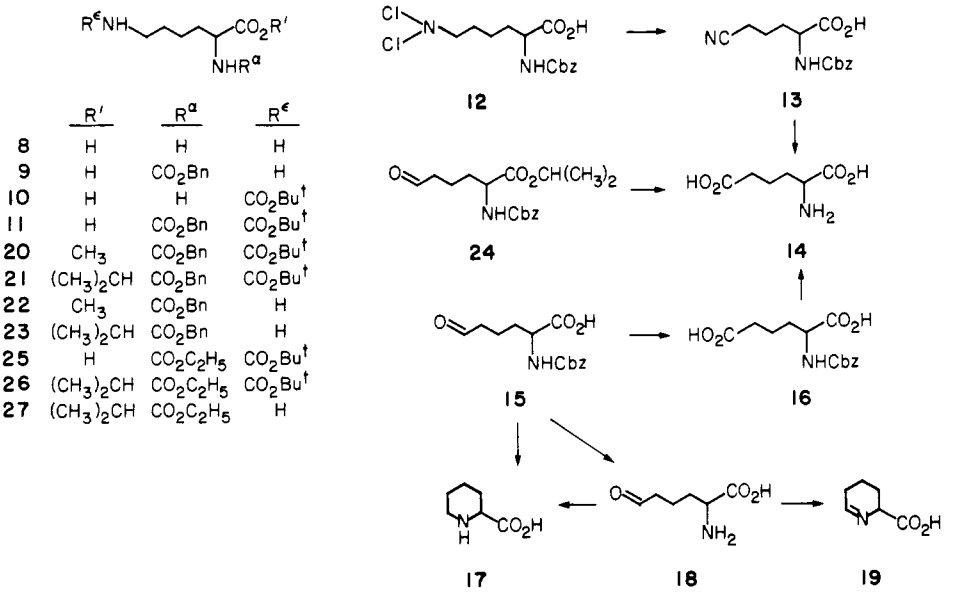
Scheme II. Oxidative Deaminations of the ε-Amino Group of Lysine



and a multitude of chemical[19,20] and enzymatic[21,22] resolution techniques. These processes require many steps and are generally inefficient. A recent procedure[7] began with N^{α}-benzyloxycarbonyllysine (**9**), which was first converted to the *N*,*N*-dichloro derivative **12**. Exhaustive dehydrohalogenation afforded nitrile **13**, which after hydrolysis in strong acid yielded the desired α-amino acid **14** in 30% yield from **9**. The procedure developed here also employs **9**, which is prepared[23] more efficiently from the N^{ϵ}-*tert*-butyloxycarbonyl derivative **10**. Conversion to optically pure α-aminoadipic acid (**14**) was then achieved in two stages. Oxidation of the ε-amino group of **9** to the resulting aldehyde **15** was achieved in high yield. Acidic hydrolysis of the α-carbamate of **16** then provided the desired fully deprotected amino acid. Catalytic reduction of aldehyde **15** afforded optically pure pipecolic acid (**17**) in a straightforward fashion. In both situations the clean separation of aldehyde **15** from the hydrolytic medium facilitated the subsequent manipulation of these polar intermediates.

Due to the interest in Δ^1-piperideine-6-carboxylic acid (**19**) as an intermediate in several biological systems,[24-27] we attempted to intercept this highly unstable compound, which has been prepared with limited success by a number of different routes.[28-30] An attempt to remove the α-benzyloxycarbonyl group with Pd/C and hydrogen at atmospheric pressure resulted in the expected cyclization of amino aldehyde **18**. However, overreduction could not be avoided with these techniques. Transfer hydrogenation (1,4-cyclohexadiene in ethyl acetate with Pd/C) afforded similar results. Attempts to remove the benzyloxycarbonyl group hydrolytically by using hydrochloric acid resulted in gross polymerization.[30,31]

The conversion of α-protected lysine esters (examples 8 and 9, Table I) was also examined and found to be preparatively useful. N^{ϵ}-*t*-Boc-N^{α}-Cbz-lysine (**11**) was converted to the intermediate acid chloride followed by addition of methanol and 2-propanol, affording esters **20** and **21**, respectively. Cold TFA removed the *t*-Boc group and yielded the corresponding ε-amino esters **22** and **23**. Methyl ester **22** underwent intramolecular cyclization to some extent, forming the seven-membered lactam; however, this problem was avoided with the isopropyl ester **23**. As a result, reaction of amino ester **23** with the pyridinium aldehyde **4** proceeded smoothly, affording the desired aldehyde ester **24**. Oxidation followed by exhaustive acid hydrolysis yielded optically pure α-aminoadipic acid (**14**). Catalytic reduction of **24** resulted in the formation of pipecolic acid (**17**) as its isopropyl ester, presumably via the Δ^1 intermediate **19**. Similarly, removal of the blocking group after oxidation of **24** could afford a valuable intermediate for the preparation of optically active regiospecific mixed esters of α-aminoadipic acid.

In an effort to minimize loss of the α-amino protecting group, the corresponding α-ethoxycarbonyl compound **25** was prepared. Conversion to its isopropyl ester **26** and subsequent N^{ϵ}-deblocking afforded the desired amine **27**, which was then converted to α-aminoadipic acid via the techniques described above.

Summary

Several features contribute to the overall efficiency of this reaction scheme. Initial Schiff-base formation occurs readily due to the susceptibility of the 4-carboxaldehyde to nucleophilic attack. The electron-deficient quaternary pyridine moiety greatly increases the ease of subsequent deprotonation. Similarly, anion electron density is focused upon the original aldehydic carbon. As a consequence, reprotonation occurs at this preferred site, leading to essentially complete prototropic rearrangement. Mild acid-catalyzed hydrolysis of the new Schiff base thus results in formation of a new carbonyl species. The overall oxidative conversion may be quickly and efficiently performed in one flask with minimal purification required for the desired products. A most notable feature of this transformation scheme is its compatibility with a large variety of functional groups. We are particularly interested

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in conserving existing chirality as well, and this methodology has demonstrated that capability with a number of substrates.

Experimental Section

General Procedures. Infrared spectra were obtained with a Perkin-Elmer 137 spectrohotometer. NMR spectra were recorded with Varian T-60, UCB 200-MHz and UCB 250-MHz instruments. Samples were prepared in $CDCl_3$ unless otherwise stated. Gas chromatographic data were obtained with a Hewlett-Packard 402 chromatograph. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Normal-phase HPLC analysis was conducted with an Altex 110A dual pump system coupled with a Hitachi 100-30 spectrophotometer and a 5 μm (3.2 × 250 mm) Spherisorb S1 column.

Transamination Reactions. To a magnetically stirred mixture of amine (3.0 mmol) in CH_2Cl_2/DMF (30 mL, 3/1) at room temperature was added 4-formyl-1-methylpyridinium benzenesulfonate (1.0 g, 120 mol%) in one portion. After total consumption of the amine (TLC, 5–10 min), the reaction solution was treated with an organic base (100 mol %), stirred for 5 min, and quenched with cold saturated aqueous oxalic acid (30 mL). Stirring was continued for 0.5–1 h, and the reaction was then diluted with H_2O (50 mL) and Et_2O (100 mL). After several ether extractions, the combined organic phase was dried ($MgSO_4$), filtered, and evaporated to afford the crude carbonyl compounds desired.

4-Formyl-1-methylpyridinium Benzenesulfonate (4). This pyridinium salt was prepared in a manner similar to that reported[15] in 83% yield as a hygroscopic white solid. Freshly distilled (bulb to bulb) pyridine-4-carboxaldehyde and methyl benzenesulfonate were heated in refluxing benzene (N_2) for 4 h, forming an oil, which was dried under high vacuum. The resulting crystals were triturated with acetone, collected with suction, and dried in vacuo at 50 °C for 12 h: mp 100–101 °C; IR (Nujol) 1700 (s), 1640 (s), 695 (s) cm^{-1}; NMR (Me_2SO_2-d_6) δ 4.40 (s, 3 H), 7.15 (m, 3 H), 7.40 (m, 2 H), 8.24 (d, 2 H, J = 6 Hz), 9.12 (d, 2 H, J = 6 Hz), 10.08 (s, 1 H). Anal. Calcd for $C_{13}H_{13}NO_4S$: C, 55.9; H, 4.7; N, 5.0. Found: C, 55.6; H, 4.8; N, 4.9.

***tert*-Butyl 7-α-Hydroxydeacetoxycephalosporanate.** This cephalosporin derivative was prepared from *tert*-butyl 7-aminodeacetoxycephalosporanate.[32] Transamination was conducted as described above with Et_3N for Schiff-base deprotonation. The unstable α-keto-β-lactam intermediate was directly reduced at room temperature with $NaCNBH_3$ (50 mol %) in 2-propanol, maintaining a pH of 5–6 by periodic dropwise additions of acetic acid. Conventional isolation afforded the α-hydroxy derivative as a crystalline solid in 73% yield: mp 149–150 °C; IR ($CHCl_3$) 3450 (m, b), 1775 (s), 1720 (s) cm^{-1}; NMR δ 1.55 (s, 9 H), 2.13 (s, 3 H), 3.34 (2 H, AB q, J_{AB} = 18 Hz, $\Delta\nu$ = 52, δ_A = 3.47, δ_B = 3.21), 3.37 (d, 1 H, J = 9 Hz), 4.95 (d, 1 H, J = 4.5 Hz), 5.26 (dd , 1 H, J_{AX} = 9 Hz, J_{BX} = 4.5 Hz). Anal. Calcd for $C_{12}H_{17}NO_4S$: C, 53.1; H, 6.3; N, 5.2. Found: C, 52.8; H, 6.3; N, 5.1.

***N*-Benzyloxycarbonyl-D-glucosamine** was prepared as described[33] in nearly quantitative yield as a white crystalline solid: mp 212–213 °C (lit.[33] mp 214 °C); $[\alpha]^{23}_D$ +63.0° (c 3.4, pyridine (lit.[33] $[\alpha]$ + 62.8°).

1,3,4,6-Tetra-*O*-acetyl-2-*N*-benzyloxycarbonyl-D-glucosamine was prepared by heating *N*-benzyloxycarbonylglucosamine (3.01 g, 10 mmol) at 85 °C with 20 mL of acetic anhydride containing 4 g of anhydrous NaOAc. After 3 h, the reaction mixture was poured into cold water (200 mL), stirred vigorously for 4 h, and diluted with CH_2Cl_2 (100 mL). The phases were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the organic layers were combined to afford, after chromatography (SiO_2), the β anomer (0.83 g, 18%) and the α anomer (3.32 g, 70%). α anomer: mp 106–108 °C; IR (Nujol) 3350 (m), 1750 (s), 1695 (s) cm^{-1}; NMR δ 1.92 (s, 3 H), 2.00 (s, 6 H), 2.05 (s, 3 H), 3.62–4.50 (m, 4 H), 5.05 (s, 2 H), 4.78–5.62 (m, 3 H), 5.60 (d, 1 H, J = 8 Hz), 7.27 (s, 5 H); $[\alpha]^{23}_D$ +75.3° (c 2, pyridine). β anomer: mp 151–152 °C (lit.[34] mp 150–151 °C); IR (Nujol) 3340 (m), 1750 (s, b), 1705 (s) cm^{-1}; NMR δ 1.88 (s, 3 H), 1.98 (s, 3 H), 2.03 (s, 3 H), 2.12 (s, 3 H), 3.75–4.45 (m, 4 H), 5.01 (s, 2 H), 4.77–5.42 (m, 3 H), 6.08 (d, 1 H, J = 4 Hz), 7.22 (s, 5 H); $[\alpha]^{23}_D$ +21.6° (c 2, pyridine) (lit.[34] $[\alpha]$ +21.5°).

1,3,4,6-Tetra-*O*-α-D-glucosamine was quantitatively prepared by catalytic hydrogenolysis (Pd/C/H_2, 55 psi, MeOH) of its *N*-benzyloxycarbonyl precursor: mp 114–116 °C; IR (Nujol) 3350 (w), 3250 (w), 1750 (s, b) cm^{-1}; NMR δ 1.58 (bs, 2 H), 2.00 (s, 3 H), 2.03 (s, 3 H), 2.07 (s, 3 H), 2.15 (s, 3 H), 2.79–3.32 (m, 1 H), 3.80–4.47 (m, 3 H), 4.79–5.32 (m, 2 H), 6.04 (d, 1 H, J = 3 Hz); $[\alpha]^{23}_D$ +134.2° (c 2, pyridine). Anal. Calcd for $C_{14}H_{21}NO_9$: C, 48.4; H, 6.1; N, 4.0. Found: C, 48.4; H, 6.0; N, 4.0.

3,4,6-Tri-*O*-acetyl-D-glucosone. The oxidative conversion of 1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine to glucosone derivatives afforded mixtures whose composition depended upon the duration of hydrolysis. After a 5–10 min treatment with aqueous oxalic acid at room temperature, a 90% yield of a mixture of pyranose acetates was isolated as a light yellow resin. A 30-min hydrolysis afforded mainly the two furanose triacetates in 80% yield. However, prolonged exposure to aqueous acid resulted in total conversion to glucosone itself. The glucosone prepared by this method was identical with that obtained by a reported procedure.[16]

Infrared analysis of the two triacetate mixtures was uninformative; however, their NMR spectra were distinctive. The pyranose mixture exhibited two downfield pairs of anomeric protons (δ 6.62 and 6.19) in the ratio of approximately 2:1. Each individual pair of signals was observed in a ratio of 1:1. Thus it appears that two pyranose triacetates and two tetraacetates were formed. The C-3 methine at δ 7.05 exhibited the normal trans-diaxial coupling with the C-4-H (J = 13 Hz) as well as the pairing of pairs pattern already described. The furanose triacetates exhibited a 1:1 pair of downfield signals (δ 7.39 and 7.89). In addition, a highly symetrical pair of AB quartets (δ 3.17) was observed due to a diastereomeric acetoxymethyl coupling with the C-4 methine. In each situation it was clear that mutarotation had occurred, affording a 1:1 mixture of α and β configurations.

***N*$^{\epsilon}$-*tert*-Butyloxycarbonyl-L-lysine (10)** was prepared by the procedures described:[23] mp 257–259 °C dec (lit.[23] mp 256–258 °C); $[\alpha]^{23}_D$ +6.9° (c 1, 2 N NH_4OH) (lit.[23] $[\alpha]$ +6.8°).

***N*$^{\alpha}$-Benzyloxycarbonyl-*N*$^{\epsilon}$-*tert*-butyloxycarbonyl-L-lysine (11)** was prepared as a heavy yellow resin (94%) by treating *N*$^{\epsilon}$-*tert*-butyloxycarbonyl-L-lysine (**10**) with benzyl chloroformate (115 mol%) in aqueous alkali. It was used without further purification. However, it was characterized as the dicyclohexylammonium salt:[23] mp 154–155 °C (lit.[23] mp 154.5–155 °C); $[\alpha]^{23}_D$ +8.0° (c 1, EtOH) (lit.[23] $[\alpha]$ +8.1°).

***N*$^{\alpha}$-Benzyloxycarbonyl-L-lysine (9)** was prepared from the bis carbamate **11** by treatment with anhydrous TFA at 10–15 °C. After complete cleavage (TLC) had occurred, the solution was evaporated and the residue dissolved in Et_2O. After the solution had cooled to 4 °C, Et_3N was added, precipitating **9** as a white powdery salt in 89% yield: mp 217–219 °C. The free amino acid was also prepared by precipitation from water at pH 6: mp 230–232 °C (lit.[23] mp 228–230 °C); $[\alpha]^{23}_D$ −11.8° (c 2, 1 N HCl).

***N*$^{\epsilon}$-*tert*-Butyloxycarbonyl-*N*$^{\alpha}$-ethoxycarbonyl-L-lysine (25).** Reaction between ethyl chloroformate (115 mol%) and *N*$^{\epsilon}$-*t*-Boc-lysine (**10**) afforded the bis carbamate **25** as a thick light yellow oil in 96% yield: IR (film) 3250 (s, b), 1710 (s), 1675 (s, b) cm^{-1}; NMR δ 1.25 (t, 3 H, J = 8 Hz), 1.48 (s, 9 H), 1.3–2.15 (m, 6 H), 3.13 (m, 2 H), 4.13 (q, 2 H, J = 8 Hz), 4.25 (m, 1 H), 5.05 (s, 1 H), 5.73 (bd, 1 H, J = 7 Hz), 9.90 (s, 1 H); $[\alpha]^{23}_D$ +6.7° (c 2, CH_2Cl_2). Anal. Calcd for $C_{14}H_{26}N_2O_6$: C, 52.8; H, 8.2; N, 8.8. Found: C, 52.7; H, 8.0; N, 8.7.

***N*$^{\epsilon}$-*tert*-Butyloxycarbonyl-*N*$^{\alpha}$-ethoxycarbonyl-L-lysine Isopropyl Ester (26).** To a cold (0 °C) magnetically stirred solution (CH_2Cl_2, N_2) of bis carbamate acid **25** was added oxalyl chloride (110 mol %) in one portion together with dry DMF (5 mol%). After 1 h, the solution was evaporated, the yellow residue was redissolved in dry CH_2Cl_2, and 2-propanol (1000 mol%) was added at room temperature. After the mixture was stirred for 1 h, the usual extractive isolation afforded ester **26** as a light yellow oil in 93% yield: IR (neat) 3350 (m), 1710 (s, b) cm^{-1}; NMR δ 1.22 (t, 3 H, J = 8 Hz), 1.25 (d, 6 H, J = 6 Hz), 1.45 (s, 9 H), 1.3–2.0 (m, 6 H), 3.06 (m, 2 H), 4.06 (q, 2 H, J = 8 Hz), 4.16 (m, 1 H), 4.96 (heptet, 1 H, J = 6 Hz), 5.05 (d, 1 H, J = 6 Hz), 5.58 (d, 1 H, J = 8 Hz); $[\alpha]^{23}_D$ +4.6° (c, 2, CH_2Cl_2). Anal. Calcd for $C_{17}H_{32}N_2O_6$: C, 56.6; H, 8.9; N, 7.8. Found: C, 56.3; H, 8.7; N, 7.6.

***N*$^{\alpha}$-Ethoxycarboxyl-L-lysine isopropyl ester (27)** was prepared from **26** as described for the preparation of *N*$^{\alpha}$-benzyloxycarbonyl-L-lysine (**9**) from **11**. Normal extractive isolation afforded **27** as a light yellow oil in 95% yield: IR (neat) 3270 (s, b), 1695 (s, b) cm^{-1}; NMR δ 1.25 (t, 3 H, J = 8 Hz), 1.27 (d, 6 H, J = 6 Hz), 1.2–2.1 (m, 8 H), 2.65 (m, 2 H), 4.06 (q, 2 H, J = 8 Hz), 4.05 (m, 1 H), 4.95 (heptet, 1 H, J = 6 Hz), 6.10 (s, 1 H); $[\alpha]^{23}_D$ +5.5° (c 2, CH_2Cl_2).

Isopropyl α-benzyloxycarbonylamino-ϵ-oxohexanoate (24) was prepared as described for the general transamination sequence. The aldehyde **24** was isolated as a heavy yellow oil in 96% yield: IR (neat) 1735 (s), 1710 (s, b), 1650 (s) cm^{-1}; NMR δ 1.28 (d, 6 H, J = 7 Hz), 1.31 (t, 3 H, J = 8 Hz), 1.5–2.6 (m, 6 H), 4.18 (q, 2 H, J = 8 H), 4.82 (m, 1 H), 4.90 (heptet, 1 H, J = 7 Hz), 6.81 (t, 1 H, J = 7 Hz); $[\alpha]^{23}_D$ −14.5° (c 2, CH_2Cl_2).

Without further purification, this product was converted at room temperature to the corresponding half acid via Jones oxidation in acetone. After the reaction was quenched with 2-propanol, the intermediate acid was isolated by extraction. Hydrolysis by heating in 6 N HCl afforded optically pure α-aminoadipic acid, which precipitated from water at pH 3 in 92% yield.

(32) We are indebted to Dr. George Dunn of Smith, Kline and French Laboratories for a generous sample of this compound.

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N^{α}-Benzyloxycarbonyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysine isopropyl ester (21) was prepared from **11** in the manner described for the preparation of the corresponding N^{α}-ethoxycarbonyl compound **26** in 88% yield: IR 3260 (m), 1685 (s, b) cm^{-1}; NMR δ 1.25 (d, 6 H, J = 6 Hz) 1.46 (s, 9 H), 1.1–2.05 (m, 6 H), 3.06 (m, 2 H), 4.24 (m, 1 H), 4.85 (d, 1 H), 4.97 (heptet, 1 H, J = 7 Hz), 5.07 (s, 2 H), 5.62 (d, 1 H, J = 8 Hz), 7.24 (s, 5 H); $[\alpha]^{23}_D$ +2.6° (c 2, CH_2Cl_2). Anal. Calcd for $C_{22}H_{34}N_2O_6$: C, 62.5; H, 8.1; N, 6.6. Found: C, 62.3; H, 8.0; N, 6.6.

N^{α}-Benzyloxycarbonyl-L-lysine isopropyl ester (23) was prepared from the corresponding N^{ϵ}-*t*-Boc derivative **21** by the method employed for the preparation of N^{α}-benzyloxycarbonyl-L-lysine (**9**), affording **23** as a light yellow oil in 93% yield: IR (neat), 3330 (s), 1720 (s, b) cm^{-1}; NMR δ 1.21 (d, 6 H, J = 7 Hz), 1.05–2.04 (m, 8 H), 2.62 (m, 2 H), 4.23 (m, 1 H), 4.93 (heptet, 1 H, J = 7 Hz), 5.17 (s, 2 H), 5.77 (b d, 1 H), 7.28 (s, 5 H); $[\alpha]^{23}_D$ +4.9° (c 1, CH_2Cl_2).

Determination of Optical Purity of Lysine Transamination Products. The α-aminoadipic acids were fused (170 °C, 30 min) to afford 2-piperidone-6-carboxylic acid as a crystalline solid in 85% yield: mp 105–107 °C; IR (mull) 3345 (m), 2500 (m), 1725 (s) cm^{-1}; NMR δ 1.6–2.25 (m, 4 H), 2.18 (t, 2 H, J = 6 Hz), 4.12 (t, 1 H, J = 6 Hz); $[\alpha]^{23}_D$ −15.8° (c 1, 1 N NaOH). Anal. Calcd for $C_6H_9NO_3$: C, 50.3; H, 6.3; N, 9.8. Found: C, 50.2; H, 6.3; N, 9.6.

The 2-piperidone-6-carboxylic acid was then converted to its acid chloride by treatment with oxalyl chloride (105 mol %) and DMF (5 mol %) in CH_2Cl_2 at room temperature for 1 h. (+)-α-Phenylethylamine was then added, and the resulting amide, after the usual extractive isolation, was analyzed by HPLC. This procedure was also repeated with racemic α-aminoadipic acid to establish the resolution and detection limits of the diastereomeric amides: HPLC, 1:1 CH_2Cl_2/isooctane; D-2-piperidone-6-carboxamide, R_t 35.5 min; L-2-piperidone-6-carboxamide, R_t 38.5 min.

The pipecolic acids were converted to their corresponding N-ethoxycarbonyl derivatives. Preparation of their acid chlorides and subsequent conversion to diastereomeric amides with (+)-α-phenylethylamine were readily achieved as described above: 1:1 CH_2Cl_2/isooctane; D-N-ethoxycarbonylpipecolic acid amide, R_t 19 min; L-N-ethoxycarbonylpipecolic acid amide, R_t 21.5 min.

In each instance, with limits of detection established as less than 1%, none of the D diastereomer was observed. Hence the transamination sequence as well as the following transformations were achieved with complete retention of stereochemistry at the lysine α-carbon.

Registry No. 4, 82228-89-5; **9**, 2212-75-1; **10**, 2418-95-3; **11**, 2389-60-8; **11** dicyclohexylammonium salt, 2212-76-2; (*S*)-**14**, 1118-90-7; (*S*)-**17**, 3105-95-1; **21**, 82228-90-8; **23**, 47307-39-1; **24**, 82228-91-9; **25**, 82228-92-0; **26**, 82228-93-1; **27**, 82228-94-2; pyridine-4-carboxaldehyde, 872-85-5; methyl benzenesulfonate, 80-18-2; *tert*-butyl 7-α-hydroxydeacetoxycephalosphoranate, 63599-56-4; *tert*-butyl 7-aminodeacetoxycephalosphoranate, 33610-06-9; N-benzyloxycarbonyl-D-glucosamine, 16684-31-4; β-1,3,4,6-tetra-*O*-acetyl-2-N-benzyloxycarbonyl-D-glucosamine, 35946-66-8; α–1,3,4,6-tetra-*O*-acetyl-2-N-benzyloxycarbonyl-D-glucosamine, 82264-19-5; 3,4,6-tri-*O*-acetyl-D-glucosone, 82228-95-3; (*S*)-2-piperidone-6-carboxylic acid, 34622-39-4; pentylamine, 110-58-7; pentanal, 110-62-3; cyclohexylamine, 108-91-8; cyclohexanone, 108-94-1; α-phenylethylamine, 98-84-0; acetophenone, 98-86-2; β-phenylethylamine, 64-04-0; phenylacetaldehyde, 122-78-1; 1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine, 17460-45-6.

One-Electron Chemical Reductions of Phenylalkylsulfonium Salts

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Abstract: Twenty-two arylalkylsulfonium salts have been reduced with potassium in graphite in tetrahydrofuran and the sulfide products identified. Two trialkylsulfonium salts did not reduce under these conditions. Comparison of the sulfides from a series of monophenylalkylsulfonium salts reveals a leaving-group propensity of benzyl > secondary > primary > methyl > phenyl in a ratio of 28:(6.0 ± 0.3):1.0:(0.53 ± 0.09):<0.05. The cleavage ratio is shown to be independent of the electron source and the homogeneity of heterogeneity of the reaction in two cases. Multiplicative transitivity of the above ratios is not observed, although the same qualitative order is found for other comparisons. These results are interpreted in terms of the initial formation of a π-ligand radical anion sulfonium cation, which undergoes cleavage to a carbon radical and a sulfide. This appears to be the first evidence for this type of structure in a sulfur system. Leaving-group propensities different from the above order are observed in reductions of diphenylsulfonium and benzo-fused sulfonium salts, and rationales are offered. The intermediates in these reactions appear to be different from those involved in radical additions to, or displacements on, sulfur.

The prospect that one-electron reductions of sulfonium salts could serve as a convenient source of a variety of radicals, along with the possibility that one-electron reductions of sulfonium salts could explain reactions attributed to other pathways, prompted our investigation of the chemical reduction of a series of sulfonium salts.

Most of the one-electron reductions of sulfonium salts that have been reported are electrochemical studies[1-9] in which, with some exceptions,[4,9] an irreversible one-electron transfer is followed by reactions with cathodic material and/or the formation of a carbon radical and a sulfide. The radicals are converted to products by further reaction and/or reduction. A similar formation of radicals has also been noted in reactions of triarylsulfonium salts with potential nucleophiles.[10]

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