tion of the L tripeptide began: the small fraction was collected, which melted at 119.2–119.7° (lit.[21] mp 116.5–119.5°). Continuous refrigeration gave more crystals of the same material. The residual peptide was obtained by reducing the volume of the solution amounting to 3.50 g, and about 0.26 g of oil was left uncrystallized: ir (Nujol mull) 3225, 1750, 1715, 1688, 1665, 1650 cm^{-1} (all sharp); nmr ($CDCl_3$) δ 1.20 (t, CH_3, 3 H), 3.05 (d, CH_2, 2 H), 3.70–3.93 (two d, CH_2, 4 H), 4.10 (q, CH_2, 2 H), 4.83 (d, CH, 1 H), 5.05 (s, CH_2, 2 H), 5.85 (br, NH, 1 H), 7.15 (br, NH, 1 H), 7.15 (s, phenyl ring, 5 H), and 7.30 (s, phenyl ring, 5 H).

Anal. Calcd for $C_{23}H_{27}N_3O_5$ (441.47): C, 62.57; H, 6.17; N, 9.52. Found: C, 62.80; H, 6.04; N, 9.40.

The above procedure was followed with 3.56 g (0.01 mol) of *N*-benzyloxycarbonylglycyl-L-phenylalanine, 3.30 g (0.011 mol) of *N*-isopropyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate, and 1.15 g (0.011 mol) of ethyl glycinate in 30 ml of tetrahydrofuran. The yield of the amorphous tripeptide derivative was 4.30 g (97%). A 2% solution of the peptide in absolute ethanol gave, after about 3 weeks of refrigeration, the first fraction of crystals amounting to 0.13 g (3%) of DL tripeptide melting at 129–130° (lit.[21] mp 132–133°). After 2 days 0.07 g of crystals was obtained melting at 120–121°, and soon the L tripeptide began to appear amounting to 3.12 g, melting at 119–120.5°. The residue was obtained in crude crystals. The elemental analysis of this product was identical with that of the product in the first part of this synthesis.

Registry No.—**1**, 51157-30-3; **2**, 51056-73-6; **3**, 51108-18-0; **4**, 51056-75-8; **5**, 51056-77-0; **6**, 51056-79-2; **7**, 51056-81-6; **8**, 51056-83-8; **9**, 51056-85-0; **10**, 51056-87-2; **11**, 51108-20-4; **12**, 51056-89-4; triethylamine, 121-44-8; *N*-ethylpiperidine, 766-09-6; *N,N*-dimethylcyclohexylamine, 98-94-2; pyridine, 110-86-1; *N*-*n*-propylpiperidine, 5470-02-0; *N*-*n*-butylpiperidine, 4945-48-6; ethyl chloroformate, 541-41-3; benzyl chloroformate, 501-53-1; isobutyl chloroformate, 543-27-1; *sec*-butyl chloroformate, 17462-58-7; isopropyl chloroformate, 108-23-6; cyclohexylamine, 108-91-8; *N*-methylcyclohexylamine, 100-60-7; *N*-benzyloxycarbonylglycine, 1138-80-3; *N*-benzyloxycarbonyl-DL-valylglycine ethyl ester, 7801-65-2; *N*-benzyloxycarbonyl-DL-valine, 3588-63-4; *N*-benzyloxycarbonyl-DL-valylglycylglycine ethyl ester, 51056-90-7; *N*-benzyloxycarbonylglycyl-L-phenylalanine, 1170-76-9; *N*-benzyloxycarbonylglycyl-L-phenylalanylglycine ethyl ester, 2073-59-8.

References and Notes

(1) Financial support from the National Science Foundation to the Department of Chemistry for the purchase of XL-100-15 and T-60 nmr spectrometers is gratefully acknowledged.

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N-Acyl-*N,N,N*-Trialkylammonium Fluoroborates. Synthesis and Reactions

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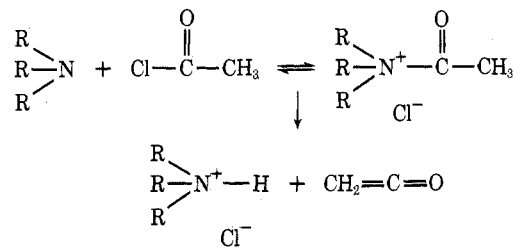
Stable *N*-acyl-*N,N,N*-trialkylammonium fluoroborates have been prepared from tertiary amines and acyl halides followed by exchange of anion to fluoroborate with HF/BF_3. The stable salts react with various nucleophiles such as amines, acids, alcohols, and thiols to form the acylated derivatives. The primary alcohols react rapidly, the secondary alcohols only partially, and tertiary alcohols do not react at all.

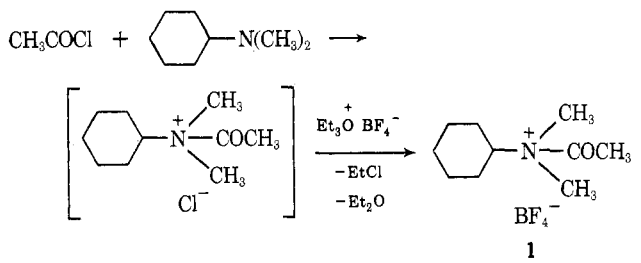
N-Acyl-*N,N,N*-trialkylammonium salts have been examined extensively for a variety of purposes.[3-6] The salts that have been examined have been highly reactive and quite frequently impure, precluding detailed examination of their structure and properties.[7-13] The best evidence was obtained by ir from adducts prepared at liquid nitrogen temperatures.[14] However, even these showed adsorptions at around 2300–2700 cm^{-1}, indicating that the hydrohalides were present.[15] Preparation by alkylation of amides was only partially successful.[16] Thus while the compounds have been prepared in impure form many times and have been assumed as intermediates in many other reactions,[17-20] very little can be accepted without some reservations.

Our interest in *N*-cyano- and *N*-alkyloxycarbonyl *N,N,N*-trialkylammonium salts[2] as reagents in peptide synthesis led us to consider *N*-acylammonium salts as possible reagents for preparation of protecting groups. In *N*-acylammonium salts the size of the tertiary amine can be readily varied, thus allowing the possibility of stereoselective acylating reagents. We assumed from our previous experience[2] that the major cause of instability was the nucleophilic nature of the anion, which could regenerate the tertiary amine, thus allowing dehydrohalogenation

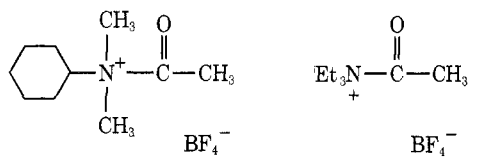
reactions.[4] We chose to convert the unstable salts to the considerably more stable fluoroborates.



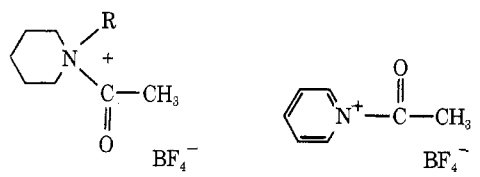
The use of triethyloxonium fluoroborate as the exchange reagent[1] was satisfactory when the tertiary amine was *N,N*-dimethylcyclohexylamine, giving 87% of *N*-acetyl-*N,N*-dimethylcyclohexylammonium fluoroborate. How-



ever, the treatment of the adducts of other tertiary amines, such as triethylamine, *N*-ethylpiperidine, and pyridine, gave mixtures containing the hydrohalide salts. When a mixture of HF/BF_3 was used as the anion exchange reagent,[2] colorless crystals of *N*-acetylammonium fluoroborates were obtained. They were stable under ether or as solids in a dry atmosphere at room temperature. The compounds **1–6** were recrystallizable from anhydrous organic solvents and were obtained in 85–98% yield except acetylpyridinium fluoroborate (**6**), where a large amount of pyridinium hydrofluoroborate was removed by washing with dry acetone, giving only 19% yield.



1 **2**



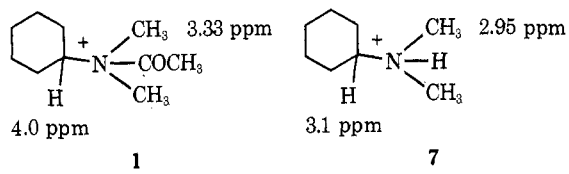
3, R = Et
4, R = *n*-Pr
5, R = *n*-Bu

6

The *N*-acetylammonium fluoroborates decomposed rather rapidly in open air. The apparently most stable salt was *N*-acetyl-*N,N*-dimethylcyclohexylammonium fluoroborate (**1**), and the pyridinium salt **6** was the least stable. All of the salts were soluble in acetonitrile and all except the salts **2** and **6** were soluble in acetone. The salt **6** was soluble in trifluoroacetic acid, but reacted slowly to form unidentified products as observed by nmr spectroscopy.

The infrared spectra of the *N*-acetylammonium fluoroborates showed a strong carbonyl bond absorption at around 1806–1826 cm^{-1}, somewhat higher than that of acetyl chloride, which occurs at 1807 cm^{-1}.[21] This is in agreement with the observation made by Cook,[14] and explainable as being due to the presence of the positive charge on the nitrogen atom in the obtained compounds.

Nuclear magnetic resonance spectra of *N*-acetylammonium fluoroborates **1–6** exhibited signals for the acetyl groups appear at about δ 2.85–2.90 ppm in acetone-d_6 and at around δ 2.70–2.80 ppm in acetonitrile. These chemical shifts are generally lower by about 0.1 ppm than that of acetyl chloride in similar solvents. The acetyl group of *N*-acetylpyridinium fluoroborate (**6**) appeared at δ 3.13 ppm in trifluoroacetic acid and at δ 3.01 ppm in acetonitrile. The presence of the acetyl group in *N*-acetylammonium fluoroborates also produced a considerable downfield shift of methine, methylene, and methyl protons adjacent to the nitrogen atom. The chemical shifts of the methine and methyl protons of compounds **1** and **7** are indicative,

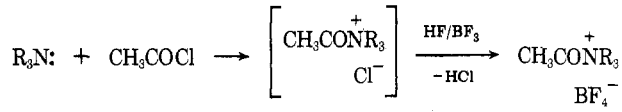


1 **7**

where the presence of the acetyl group on the nitrogen atom is apparent. The methylene protons of *N*-acetylammonium fluoroborates appeared at around δ 3.4–4.4 ppm in acetone-d_6, and these values are about 0.5–0.6 ppm lower than that of methylene protons of the corresponding ammonium salts. The ring protons of *N*-acetylpyridinium fluoroborate (**6**) appeared in three groups, and the C_2 protons are assigned to the doublet at δ 9.47 ppm in trifluoroacetic acid. The similar protons of pyridinium hydrofluoroborate salt appeared at about 0.6 ppm higher, indicating that the acetyl group on the nitrogen atom shifted the adjacent hydrogens. (The C_2 protons of *N*-acetylpyridinium hexafluoroantimonate appeared at δ 8.17 ppm in liquid sulfur dioxide at $-60°$.[22])

Although the ionic nature of the *N*-acetylammonium fluoroborates was not tested by a more direct method, the infrared and nmr spectroscopic results and physical properties such as solubility are those of ionic compounds. Thus it seems certain that the structural assignment of *the N-acetylammonium fluoroborates is correct.*

It is noteworthy that the addition of HF/BF_3 mixture to the adducts of acetyl chloride and tertiary amines did not bring about the formation of the tertiary amine hydrofluoroborates. This indicates that the adduct-forming equilibrium is complete to the side of the *N*-acetylammonium chlorides. The general similarity of some pertinent absorptions in the infrared spectra of the *N*-acetylammonium fluoroborates and the adducts of acetyl halides and tertiary amines observed by Cook[14] indicates that the adducts **8** are ionic. The general course of reaction can be represented as shown below.



8

Tri-*n*-butylamine, *N,N*-dimethyl-*tert*-butylamine, other hindered amines, and *N,N*-dimethylaniline appeared to react with acetyl chloride but on addition of HF/BF_3 gave only the ammonium salts. The same result was observed with triethylamine and benzoyl chloride, pivaloyl chloride, or *n*-butyryl chloride. With trimethylamine and *N*-methylpiperidine the adduct formation of the amines and acetyl chloride appeared to be complete but the *N*-acetylammonium fluoroborates never formed or if formed were too reactive for isolation.

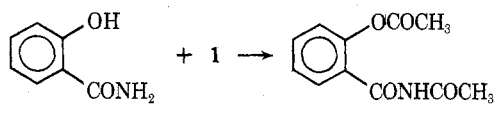
Reactions to test the acylating ability of the *N*-acetylammonium fluoroborates were tried to determine if the pure products differed in any form from the addition compounds of tertiary amines and acyl chloride. The reaction of water with the adduct of pyridine and acetyl chloride has been known to give acetic acid and acetic anhydride.[7] The same adduct was found to be a good acetylating agent for alcohols and phenols,[23] and suggested to be an analytical reagent for the determination of active hydroxyl groups.[24] The same adduct also has been known to acetylate hydrogen sulfide[25] and primary amides.[26]

To test the reactivity of *N*-acetylammonium fluoroborates the nmr spectral changes were followed after adding a small amount of deuterium oxide. In all cases spectral changes could be observed instantly in *N*-acetyl-*N*-*n*-propylpiperidinium fluoroborate (**4**). The singlet of the acetyl group at δ 2.85 ppm disappeared, and a new peak appeared at about δ 2.3 ppm which is very similar to that of acetic anhydride. Also the multiplet at about δ 3.8 ppm moved to about δ 3.3 ppm, which corresponds to the change of the methylene protons adjacent to the nitrogen atom of the compound **4** to those of the tertiary amine hydrogen ion salt. The observed changes can be explained as being due to rapid hydrolysis of the *N*-acetylammonium salt **4** by deuterium oxide to give acetic acid, which reacted further to give acetic anhydride.

The most stable *N*-acetylammonium fluoroborate (**1**) was chosen as the model compound for a large-scale product study. The nucleophiles examined were amines, thiophenol, amides, and acids.

The reaction of 25% excess of the model compound with *dl*-α-phenethylamine gave a nearly quantitative yield of crude *dl*-α-phenethylacetamide. *N*-Methylcyclohexylamine was acetylated similarly to give the acetamide in 91% yield. With *N*-methylaniline the yield of the amide was only 51%, apparently owing to some side reactions as was indicated by the appearance of a blue color in the reaction medium. Thiophenol was acetylated to give 88% of thiophenyl acetate. *N*-Benzyloxycarbonylglycine was allowed to react with the model compound, and the expected acid anhydride reacted with ethyl glycinate to give a 65% yield of the dipeptide.

The reaction of the model compound with alcohols proceeded to some extent, the degree of which depended upon the nature of the hydroxyl groups. Thus benzyl alcohol reacted to give 97% of benzyl acetate under strenuous conditions, but cyclohexanol gave only a mixture of the acetylated product and the unreacted alcohol in 68:32 ratio (by glpc) under similar reaction conditions. *tert*-Butyl alcohol could be recovered unreacted from a similar reaction. The reaction of salicylamide gave the diacetylated product as shown below.



Methylglycinate hydrochloride did not react with the model compound **1** in acetonitrile in the presence of 1 equiv of triethylamine or pyridine. Methyl benzyl ketone did not react with the model compound **1** in acetonitrile.

There might be several advantages or disadvantages in using this type of *N*-acetylammonium salts as acylation reagents. Possible disadvantages will be the low solubility in less polar organic solvents and their general instability. Although they seemed to be good acetylation reagents for strong nucleophiles, the instability did not permit the use of more strenuous reaction conditions such as high temperature for weak nucleophiles. The decreased reactivity of some *N*-acetylammonium fluoroborates toward hindered alcohols may be attributed to the bulky ammonium groups. This fact might be usefully employed for selective acetylation of less hindered hydroxyl groups.

Experimental Section[27]

Preparation of *N*-Acetyl-*N,N*-dimethylcyclohexylammonium Fluoroborate Using Triethyloxonium Fluoroborate. To a solution of 1.50 g (0.02 mol) of acetyl chloride in 50 ml of ether cooled to −78° was added in drops 1.27 g (0.01 mol) of *N,N*-dimethylcyclohexylamine in 50 ml of ether while stirring vigorously. After the completion of the addition the mixture was allowed to stand at −76° for 5 hr and at −10 to −20° for 2 hr. It was cooled again to −78°, and 1.89 g (0.01 mol) of triethyloxonium fluoroborate in 50 ml of methylene chloride cooled to −78° were added at once. After the cooling bath was removed, the solution was stirred until room temperature was reached. Precipiated colorless crystals were collected and washed with 2:1 ether–methylene chloride mixed solvent several times under a dry nitrogen atmosphere, and dried under vacuum. The yield was 2.24 g (84%); mp 64.5–66°; ir (Nujol mull) 1829 (strong, C=O and 1000–1100 cm^{-1}; nmr (acetone-d_6) δ 1.20–2.35 (br, CH_2, 10 H), 2.90 (s, CH_3CO, 3 H), 3.33 (s, CH_3N^+, 6 H), and 3.85–4.35 (br, CHN^+, 1 H).

Anal. Calcd for $C_{10}H_{20}NOBF_4$ (257.09): C, 46.72; H, 7.84; N, 5.45. Found: C, 46.70; H, 8.10; N, 5.60.

General Procedure for the Preparation of *N*-Acetyl-*N,N,N*-trialkylammonium Fluoroborates. To a solution of acetyl chloride (0.02 mol) in 50 ml of anhydrous ether cooled to −78° was added in drops a solution of tertiary amine (0.01 mol) in 50 ml of anhydrous ether while stirring. It was allowed to stand for 5 hr at −78° and for 2 hr at −10 to 20°. The adduct was cooled to −78°, and a 1:1 mixture of hydrogen fluoride and boron trifluoride (0.015 mol) was added at once. After the cooling bath was removed, the solution was stirred until room temperature was reached. Precipitated colorless crystals were collected, washed with anhydrous ether three times, and dried under vacuum. (Moisture was kept low by using a reaction system closed by calcium chloride–sodium hydroxide drying tubes where the reagents and solvents were transported by pressurized dry nitrogen. Analytical samples were prepared in a drybox.)

***N*-Acetyl-*N,N,N*-triethylammonium fluoroborate** (yield 98%) was recrystallized from 1:10 acetonitrile–ethyl acetate mixed solvent by adding anhydrous ether: mp 60–61°; ir (Nujol mull) 1814 (strong, C=O) and 1000–1120 cm^{-1}; nmr (acetonitrile) δ 1.21 (t, CH_3, 9 H), 2.72 (s, CH_3CO, 3 H), and 3.57 (q, CH_2N^+, 6 H); uv tail (acetonitrile) 240 nm (ϵ 70).

Anal. Calcd for $C_8H_{18}ONBF_4$ (231.05): C, 41.58; H, 7.85; N, 6.06. Found: C, 41.10; H, 8.14; N, 6.08.

***N*-Acetyl-*N*-ethylpiperidinium fluoroborate** (yield 90%) was recrystallized from 1:10 acetonitrile–ethyl acetate by adding anhydrous ether: mp 92–93°; ir (Nujol mull) 1817 (strong, C=O) and 980–1120 cm^{-1}; nmr (acetone-d_6) δ 1.28 (t, CH_3, 3 H), 1.50–2.20 (br, CH_2, 6 H), 2.86 (s, CH_3CO, 3 H), 3.85 (q, CH_2N^+, 2 H), and 3.40–4.15 (br, CH_2N^+, 4 H).

Anal. Calcd for $C_9H_{18}ONBF_4$ (243.06): C, 44.47; H, 7.46; N, 5.76. Found: C, 44.50; H, 7.35; N, 5.76.

***N*-Acetyl-*N*-*n*-propylpiperidinium fluoroborate** (yield 87%) was recrystallized from 1:10 acetonitrile–ethyl acetate mixed solvent by adding anhydrous ether: mp 68–69.5°; ir (Nujol mull) 1818 (strong, C=O and 990–1120 cm^{-1}; nmr (acetone-d_6) δ 0.98 (t, CH_3, 3 H), 150–2.25 (br, CH_2, 8 H), 2.85 (s, CH_3CO, 3 H), and 3.40–4.35 (br, CH_2N^+, 6 H).

Anal. Calcd for $C_{10}H_{20}ONBF_4$ (257.09): C, 46.72; H, 7.84; N, 5.45. Found: C, 46.95; H, 7.95; N, 5.58.

***N*-Acetyl-*N*-*n*-butylpiperidinium fluoroborate** (yield 99%) was recrystallized from 1:10 acetonitrile–ethyl acetate mixed solvent by adding anhydrous ether: mp 76–77°; ir (Nujol mull) 1808 (strong, C=O) and 1000–1100 cm^{-1}; nmr (acetone-d_6) δ 0.95 (t, CH_3, 3 H), 1.22–2.25 (br, CH_2, 10 H), 2.86 (s, CH_3CO, 3 H), and 3.35–4.35 (br, CH_2N^+, 6 H).

Anal. Calcd for $C_{11}H_{22}ONBF_4$ (271.12): C, 48.73; H, 8.18; N, 5.17. Found: C, 48.50; H, 8.05; N, 4.93.

***N*-Acetyl-*N,N*-dimethylcyclohexylammonium fluoroborate** (yield 97%) had ir and nmr spectra identical with those obtained earlier using triethyloxonium fluoroborate as the anion exchange reagent.

***N*-Acetylpyridinium Fluoroborate.** The reaction product was shown to contain about 40% of pyridinium fluoroborate salt as examined by nmr spectroscopy. The impurity was removed by washing with dry acetone (5 × 10 ml for 0.01 mol of product mix-

ture): mp 105–106° dec; ir (Nujol mull) 1806 (strong, C=O) and 1000–1100 cm^{-1}; nmr (CF_3COOH) δ 3.13 (s, CH_3CO, 3 H), 8.30 (t, 3-H, 2 H), 8.91 (t, 4-H, 1 H), and 9.46 (d, 2-H, 2 H).

Anal. Calcd for $C_7H_8ONBF_4$ (208.96): C, 40.23; H, 3.86; N, 6.70. Found: C, 39.90; H, 3.83; N, 7.04.

Reaction of *N*-Acetyl-*N,N*-dimethylcyclohexylammonium Fluoroborate with *N*-Methylcyclohexylamine. To a solution of 1.15 g (0.0045 mol) of *N*-acetyl-*N,N*-dimethylcyclohexylammonium fluoroborate in 20 ml of acetonitrile was added 0.60 g (0.005 mol) of *N*-methylcyclohexylamine. (Heat evolution!) The solution was allowed to stand for several hours at room temperature, and the solvent was removed on a rotary evaporator at room temperature. The residue was extracted with ether (3 × 100 ml), and the ether layer was washed with 10 ml of 1 *N* HCl solution and 10 ml of water, dried (Na_2SO_4), and evaporated on a rotary evaporator without heating to give 0.71 g (91%) of crude *N*-methylcyclohexylacetamide as residue. Short-path distillation [88° (0.9 mm)] gave 0.51 g of clear oil whose ir and nmr spectra were identical with those of *N*-methylcyclohexylacetamide.

Reaction of *N*-Acetyl-*N,N*-dimethylcyclohexylammonium Fluoroborate with *N*-Methylaniline. To a solution of 2.30 g (0.009 mol) of *N*-acetyl-*N,N*-dimethylcyclohexylammonium fluoroborate in 20 ml of acetonitrile was added 0.90 g (0.0084 mol) of *N*-methylaniline. The solution was allowed to stand overnight at room temperature. (Deep blue color appeared.) The solvent was removed on a rotary evaporator, and the residue was extracted with ether (3 × 100 ml). The ether layer was washed with 10 ml of 1 *N* HCl and 10 ml of water, dried (Na_2SO_4), and evaporated to give 0.64 g (51%) of *N*-methylacetanilide, recrystallized from ethanol: mp 99.5°; ir (Nujol mull) 1658 cm^{-1} (strong, C=O); nmr (CCl_4) δ 1.78 (s, CH_3, 3 H), 3.20 (s, CH_3, 3 H), and 7.00–7.37 (m, phenyl ring, 5 H).

Reaction of *N*-Acetyl-*N,N*-dimethylcyclohexylammonium Fluoroborate with *dl*-α-Phenethylamine. To a solution of 3.20 g (0.0125 mol) of *N*-acetyl-*N,N*-dimethylcyclohexylammonium fluoroborate in 20 ml of acetonitrile was added 1.20 g (0.01 mol) of *dl*-α-phenethylamine. The solution was allowed to stand for 1 hr, and the solvent was removed on a rotary evaporator without heating. The residue was extracted with ether (3 × 100 ml), and the ether layer was washed with 20 ml of 1 *N* HCl solution and 20 ml of water and dried (Na_2SO_4). Evaporation of the solvent gave 1.63 g (99%) of crude *dl*-α-phenethylacetamide, which was distilled [125° (0.5 mm)] to give a clear oil which crystallized later: mp 73–75°; ir (thin film) 3220 (strong, NH) and 1680 cm^{-1} (strong, C=O); nmr (CCl_4) δ 1.35 (d, CH_3, 3 H), 1.77 (s, CH_3, 3 H), 4.93 (m, CH, 1 H), 7.15 (m, phenyl ring, 5 H), and 8.33 (d, NH, 1 H).

Anal. Calcd for $C_{10}H_{13}NO$ (163.21): C, 73.59; H, 8.03; N, 8.58. Found: C, 73.31; H, 8.14; N, 8.39.

Reaction of *N*-Acetyl-*N,N*-dimethylcyclohexylammonium Fluoroborate with Thiophenol. To a solution of 1.15 g (0.0045 mol) of *N*-acetyl-*N,N*-dimethylcyclohexylammonium fluoroborate in 20 ml of acetonitrile was added 0.60 g (0.0054 mol) of thiophenol. The solution was allowed to stand for 1 day at room temperature. After refluxing for a few minutes the solvent was removed by azeotropic distillation with isopropyl ether (bp 63.5–68°), and the residue was extracted with ether (3 × 100 ml). The ether layer was washed with 20 ml of 2 N NaOH solution and 20 ml of water and dried (Na_2SO_4). Evaporation on a rotary evaporator at room temperature gave 0.60 g (88%) of crude thiophenyl acetate, which was distilled [70° (0.9 mm)] in a Hickman still to give a clear oil: ir (thin film) 1706 cm^{-1} (strong, C=O); nmr (CCl_4) δ 2.28 (s, CH_3, 3 H) and 7.30 (m, phenyl ring, 5 H); mass spectrum showed molecular ion at *m/e* 152.

Anal. Calcd for C_8H_8SO (152.21): C, 63.12; H, 5.30. Found: C, 63.35; H, 5.24.

Reaction of *N*-Acetyl-*N,N*-dimethylcyclohexylammonium Fluoroborate with Benzyl Alcohol. To a solution of 3.45 g (0.0133 mol) of *N*-acetyl-*N,N*-dimethylcyclohexylammonium fluoroborate in 20 ml of acetonitrile was added 1.26 g (0.01 mol) of benzyl alcohol. The solution was allowed to stand for 1 day at room temperature and refluxed for 30 min followed by removal of the solvent by distillation. The residue was extracted with ether (3 × 100 ml), and the ether portion was washed with water (4 × 10 ml), dried (Na_2SO_4), and evaporated on a rotary evaporator without heating to give 1.38 g (92%) of crude benzyl acetate, which was distilled in a short-path distillation column [90° (1.20 mm)] to give a clear oil: ir (thin film) 1839 (strong, C=O) and 1250 cm^{-1} (strong, CO); nmr (CCl_4) δ 1.97 (s, CH_3, 3 H), 4.97 (s, CH_2, 2 H), and 7.23 (m, phenyl ring, 5 H); mass spectrum showed molecular ion at *m/e* 150.

Anal. Calcd for $C_9H_{10}O_2$ (150.17): C, 71.98; H, 6.71. Found: C, 72.20; H. 6.62.

Reaction of *N*-Acetyl-*N,N*-dimethylcyclohexylammonium Fluoroborate with Cyclohexanol. To a solution of 3.20 g (0.0125 mol) of *N*-acetyl-*N,N*-dimethylcyclohexylammonium fluoroborate in 20 ml of acetonitrile was added 1.0 g (0.01 mol) of cyclohexanol. The solution was allowed to stand for 1 day at room temperature and for 5 hr at about 60–70°. The solvent was removed on a rotary evaporator without heating, and the residue was extracted with ether (3 × 100 ml). The ether layer was washed with a small amount of water, dried (Na_2SO_4), and evaporated to give 1.10 g of oil. Glpc analysis indicated 68% of cyclohexyl acetate and 32% of unreacted cyclohexanol (6 ft × 0.25 in., 15% Carbowax 20M on Chromosorb P, 125°, 180 ml/min). The acetate was collected and identified by ir and nmr spectra, which were in agreement with those of authentic material.

Reaction of *N*-Acetyl-*N,N*-dimethylcyclohexylammonium Fluoroborate with Salicylic Amide. To a solution of 7.71 g (0.03 mol) of *N*-acetyl-*N,N*-dimethylcyclohexylammonium fluoroborate in 50 ml of acetonitrile was added 1.30 g (0.0095 mol) of salicylic amide. The solution was allowed to stand at room temperature for 1 day followed by refluxing for about 30 min. The solvent was removed by distillation, and the residue was extracted with ether (2 × 100 ml). The ether portion was washed with a small amount of water, dried (Na_2SO_4), and distilled in a Hickman still [150° (1.4 mm)] to give 1.54 g (72.6%) of *N*-acetylsalicylic amide acetate as a clear oil which later crystallized as a low-melting solid: ir (thin film) 1779 (strong, C=O), 1718 (strong, C=O), and 1701 cm^{-1} (strong, C=O); nmr (CCl_4) δ 2.23 (s, CH_3, 3 H), 2.43 (s, CH_3, 3 H), and 6.97–7.43 (m, phenyl ring, 4 H); mass spectrum showed molecular ion at *m/e* 221.

Anal. Calcd for $C_{11}H_{11}NO_4$ (221.21): C, 59.72; H, 5.01; N, 6.35. Found: C, 60.05; H, 5.05; N, 6.56.

Reaction of *N*-Acetyl-*N,N*-dimethylcyclohexylammonium Fluoroborate with *N*-Benzyloxycarbonylglycine. To a solution of 2.30 g (0.09 mol) of *N*-acetyl-*N,N*-dimethylcyclohexylammonium fluoroborate in 20 ml of acetonitrile was added 2.09 g (0.01 mol) of *N*-benzyloxycarbonylglycine in small portions while stirring at about −10°. The solution was swirled for 15 min at −10° and for 15 min at room temperature, and cooled again to −10°. To this a solution of 1.40 g (0.01 mol) of ethyl glycinate hydrochloride and 1.01 g (0.01 mol) of triethylamine was added in drops while stirring. The reaction mixture was allowed to react and worked up as usual (as in the mixed anhydride method of peptide synthesis) to give 1.70 g (65%) of crude *N*-benzyloxycarbonylglycylglycine ethyl ester, which was recrystallized from ethanol. The final product gave identical ir and nmr spectra with those of authentic material.[1]

Registry No.—1, 51051-39-9; **2,** 51051-41-3; **3,** 51051-43-5; **4,** 51051-45-7; **5,** 51051-47-9; **6,** 51051-48-0; triethyloxonium fluoroborate, 368-39-8; acetyl chloride, 75-36-5; *N,N*-dimethylcyclohexylamine, 98-94-2; triethylamine, 121-44-8; *N*-ethylpiperidine, 766-09-6; *N*-*n*-propylpiperidine, 5470-02-0; *N*-*n*-butylpiperidine, 4945-48-6; pyridine, 110-86-1; *N*-methylcyclohexylamine, 100-60-7; *N*-methylaniline, 100-61-8; *N*-methylacetanilide, 579-10-2; *dl*-α-phenethylamine, 300-62-9; *dl*-α-phenethylacetamide, 36065-27-7; thiophenol, 108-98-5; thiophenyl acetate, 934-87-2; benzyl alcohol, 100-51-6; benzyl acetate, 140-11-4; cyclohexanol, 108-93-0; salicylic amide, 65-45-2; *N*-acetylsalicylic amide acetate, 51051-49-1; *N*-benzyloxycarbonylglycine, 1138-80-3.

References and Notes

(1) Financial support from the National Science Foundation to the Department of Chemistry for purchase of XL-100-15 and T-60 nmr spectrometers is gratefully acknowledged.
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N-Cyanoammonium Salts as Intermediates in the von Braun Cyanogen Bromide Reaction

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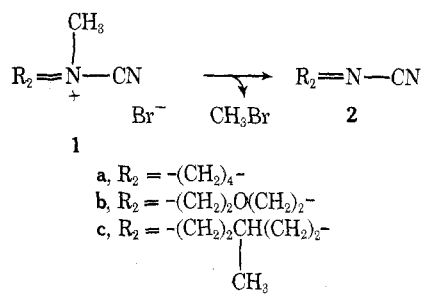
Cyanogen bromide was treated in a 1:1 ratio with a variety of tertiary amines (*e.g.*, *N*-methylpiperidine, *N*-methyl-*trans*-decahydroquinoline) to give *N*-cyanoammonium bromides (**1**), which have been trapped at temperatures of −50 to −10° for the first time, in crystalline form, and analyzed. Spontaneous decomposition of the bromides (**1**) led to methyl bromide and a secondary cyanamide (**2**). A low-temperature nmr kinetic study of step **1** → **2** in a variety of solvents yielded first-order rate constants. This two-step, low-temperature technique gave *sec*-cyanamides and, in turn, amines in yields superior to previous ones. In addition, no protection of hydroxyl groups is needed. Replacement of bromide by nonnucleophilic anions gave a number of stable cyanoammonium salts. N diastereoisomers (92:8) of *N*-cyano-*N*-methyl-*trans*-decahydroquinolinium fluoroborate (**3b** and **4b**) have been separated and their configurations determined by combined pmr, ^{13}C nmr, and X-ray crystallographic studies, whereby equatorial preference of N-cyanation was established. These stable cyanoammonium salts were then reconverted into the epimeric bromides (**3a** and **4a**), and relative reaction rates of axial cyano *vs.* equatorial cyano epimers in the step **1** → **2** were determined. Furthermore, the decomposition of the chiral intermediate, (*S*)-(+)-*N*-cyano-*N*-*sec*-butyl-4-methylpiperidinium bromide (**15a**), gave (*R*)-(−)-*sec*-butyl bromide (**16**) with inversion. Some synthetic aspects of the cyanoammonium salt intermediates are outlined.

The von Braun cyanogen bromide reaction[1] (illustrated in Scheme I) has been extensively applied[2] over the past 70 years, but no mechanistic study has been undertaken, except some early unsuccessful approaches based on analogies with triphenylphosphine–cyanogen bromide[3] or with arsines.[4] The first circumstantial evidence for the mechanism was presented by Harper, *et al.*,[5] and Casy, *et al.*,[6] respectively. Methadone, a tertiary amine containing a carbonyl group, gave with cyanogen bromide no incorporation of bromide ion, but an unexpected cyclic, nitrogen-free compound: a tetrahydrofuran derivative. Therefore, an *N*-cyanoammonium salt structure was suggested for the first time as a possible intermediate, which underwent cleavage by carbonyl oxygen as an internal nucleophile. Along similar lines Albright and Goldman[7] recently succeeded in converting different alkaloids into cyclic ethoxy cyanamides with cyanogen bromide, using ethanol as a protic solvent. The incorporation of ethoxide instead of bromide occurred, and the overall steric course was one of inversion. This is further circumstantial evidence for the same type of intermediate, with no carbon–bromide bond; displacement by alkoxide ion should have otherwise resulted in a double inversion, equaling overall retention.

Preparation of *N*-Cyanoammonium Salts. We have undertaken a different study[8a,b] with the aim of finding direct evidence by trapping the postulated cyanoammonium salts for the first time. The present paper gives a full account of the experiments we have done in this field during the last 3 years. As a preliminary approach a stable cyanoammonium salt was sought, because any nucleophilic ion would very easily result in the breaking of the rather weakened *N*-methyl or other *N*-alkyl carbon bond.

Scheme I



There was no reagent known that would contain a cyanium cation compensated by any of the known nonnucleophilic anions, such as fluoroborate. However, a complex salt of cyanogen chloride and antimony pentachloride, described by Woolf[9] in the 1950's, gave cyanogen at the cathode upon electrolysis. It thus seemed an appropriate cyanium cation donor. In the meantime ^{13}C nmr studies were undertaken[10] on this complex salt, which showed that it is certainly not a cyanium hexachloroantimonate, but has the antimony coordinated with the nitrogen, not the chlorine, of cyanogen chloride. Nonetheless, the crystalline complex salt still held the promise of being a potential CN cation donor.

Therefore, we treated $CNCl \cdot SbCl_5$ with triethylamine in nitromethane; the ir spectrum of the product showed a strong C≡N stretch around 2200 cm^{-1}. The nmr spectrum indicated a strong downfield shift (by 0.8 ppm) of the methylene protons adjacent to nitrogen, indicative of the conversion of the amine nitrogen into a quaternary