The enone isophorone (**9**) gave 3,3-dimethyl-5-oxohexanoic acid (**10**) in 86% yield.[12] Pulegone (**11**) gave a 92% yield of optically pure 3-methyladipic acid (**12**), which had been previously synthesized in unspecified yield by ozonization of pulegone.[13] A comparison of substrates **3** and **11** suggests a useful strategy: Oxidation with RuO_4 of an enone produces a dicarboxylic acid, whereas prior conversion of an enone with an alkyllithium to a tertiary allylic alcohol produces a keto acid with two different functional groups for further elaboration. (Cf. **12** with **4**.)

Experimental Section

General. All of the substrates, except **1** and **3**, are commercially available. The chemical purity of all substrates was checked by ^{13}C NMR, which showed no detectable impurities (<2%). Mass spectra were obtained on a Finnigan 4000 (quadrupole) by direct inlet to the source with an ionizing voltage of 70 eV. Both ^{1}H and ^{13}C NMR spectra were obtained on a Varian XL-100. Unless otherwise noted, all NMR samples were run in $CDCl_3$ with Me_4Si as internal reference. Optical rotations were obtained on Perkin-Elmer 141 polarimeter. Melting points are uncorrected.

(+)-3-Acetyl-2,2-dimethylcyclobutaneacetic Acid ((+)-*cis*-Pinononic Acid (8)). The oxidation of *trans*-verbenol (**7**) is representative. A stock solution was prepared from ruthenium chloride trihydrate (Aldrich), which contained 1.92 mg of $RuCl_3$/mL of H_2O. (+)-*trans*-Verbenol (**7**) ($[\alpha]^{24}_{\mathrm{D}}$ +5.7° (*c* 0.5, $CHCl_3$)) (760 mg, 5 mmol) was dissolved in 10 mL of CCl_4 and 10 mL of acetonitrile in a 100-mL, three-neck flask equipped with a condenser and magnetic stirrer. Sodium periodate (5.88 g, 27.5 mmol) was suspended in the solution with vigorous magnetic stirring. The standard rutherium chloride solution (15 mL; 28.8 mg, 0.14 mmol of $RuCl_3$) was added in one portion, and vigorous stirring was continued for 5 h. Sufficient water was then added to dissolve the separated sodium iodate. The solution was extracted with 3 × 50 mL of CH_2Cl_2, and the organic extracts were combined, dried (Na_2SO_4), and evaporated. The residue, which contained highly colored ruthenium species, was dissolved in 50 mL of diethyl ether and filtered through Celite. If necessary (usually not), residual color may be removed by stirring the ether solution with a small amount of solid $NaHSO_3$. Evaporation of the ether left 664 mg (78%) of (+)-*cis*-pinononic acid: mp 99–100 °C (CCl_4); ^{1}H NMR δ 0.98 (s, 3 H), 1.48 (s, 3 H), 1.90 (m, 1 H), 2.09 (s, 3 H), 2.44–3.01 (m, 3 H), 10.87 (s, 1 H); ^{13}C NMR δ 18.06, 18.86, 30.00, 30.31, 44.95, 45.01, 52.99, 177.89, 206.79; MS, *m/z* (relative intensity) 43 (100), 55 (26), 71 (18), 82 (22), 95 (9), 100 (8), 109 (5) 124 (2), 152 (1), 170 (<1); $[\alpha]^{25}_{\mathrm{D}}$ +18.2° (*c* 1.4, $CHCl_3$).

(+)-4-Methyl-6-oxoheptanoic Acid (4). 1,5-Dimethyl-2-(1-methylethylidene)cyclohexan-1-ol (**3**) (1.13 g, 6.0 mmol) [from (+)-pulegone (**11**); Givaudan Corp.; $[\alpha]_{\mathrm{D}}$ +23.7° (neat)] gave 0.73 g of **4** (66%) as an oil: ^{1}H NMR δ 0.95 (d, *J* = 7 Hz, 3 H), 1.62 (m, 2 H), 2.10 (m, 1 H), 2.18 (s, 3 H), 2.40 (m, 4 H), 11.25 (s, 1 H); ^{13}C NMR δ 18.84, 28.09, 29.72, 30.90, 31.11, 50.04, 178.01, 208.43; MS, *m/z* 43 (100), 55 (16), 58 (23), 69 (12), 73 (4), 83 (4), 85 (4), 97 (2), 112 (1), 125 (1), 140 (1), 158 (1); $[\alpha]^{25}_{\mathrm{D}}$ +9.3 ° (*c* 2.3, $CHCl_3$).

(−)-3-Carboxy-2,2-dimethylcyclobutaneacetic Acid ((−)-*cis*-Pinic Acid, 6). (+)-*trans*-Pinocarveol [IFF; $[\alpha]^{24}_{\mathrm{D}}$ +52.7° (*c* 0.8, $CHCl_3$)] (**5**) (500 mg, 3.2 mmol) gave 460 mg (76%) of **6**. The following changes in the standard procedure were made. After the reaction was completed, the pH was lowered to 2 with 1 N HCl. Since the final traces of ether could not easily be removed, the product was dissolved in dilute $NaHCO_3$, acidified, and extracted with 3 × 20 mL of CH_2Cl_2. This treatment gave pure **6** as an oil:[9] ^{1}H NMR δ 1.02 (s, 3 H), 1.23 (s, 3 H), 1.70–2.50 (m, 5 H), 2.74 (t, *J* = 7 Hz, 1 H), 11.63 (s, 2 H); ^{13}C NMR δ 17.61, 24.31, 29.96, 35.18, 38.01, 43.00, 46.17, 178.93, 179.21; MS, *m/z* (relative intensity) 42 (100), 45 (48), 55 (36), 69 (65), 82 (43), 100 (71), 114 (29), 124 (2), 140 (10), 150 (1), 16 8 (3); $[\alpha]^{25}_{\mathrm{D}}$ −4.9 (*c* 0.3, $CHCl_3$).

3,3-Dimethyl-5-oxohexanoic Acid (10). Isophorone (**9**) (1.11 g, 3.0 mmol) gave 1.09 g (86%) of **10** as an oil: ^{1}H NMR δ 1.00 (s, 6 H), 2.02 (s, 3 H), 2.38 (s, 2 H), 2.49 (s, 2 H), 11.34 (s, 1 H); ^{13}C NMR δ 27.81, 31.62, 32.23, 44.19, 52.04, 177.50, 208.41; MS, *m/z* (relative intensity) 43 (100), 58 (19), 70 (4), 83 (12), 101 (7), 112 (4), 125 (1), 140 (1), 158 (4).

(+)-3-Methyladipic Acid (12). (+)-Pulegone (1.07 g, 7.0 mmol) gave 1.03 g (92%) **12** as a solid: mp 85–87 °C; ^{1}H NMR δ 1.03 (d, *J* = 6 Hz, 3 H), 1.40–2.20 (m, 3 H), 2.35 (m, 4 H), 10.6 (s, 2 H); ^{13}C NMR (Me_2SO) δ 19.57, 29.71, 31.61, 31.78, 41.40, 174.05, 174.76; MS, *m/z* (relative intensity) 41 (100), 45 (64), 55 (78), 59 (39), 69 (19), 73 (12), 83 (22), 101 (13), 114 (15), 142 (2), 160 (<1); $[\alpha]^{25}_{\mathrm{D}}$ +9.5° (*c* 0.8, $CHCl_3$).

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Halide Exchange Reactions between Aryl Halides and Alkali Halides Catalyzed by Nickel Metal

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The application of metal powders in organic and organometallic synthesis has attracted considerable interest in recent years.[1-4] However, most of the investigations were focused on activated metal powders prepared by special methods. There is little work concerning the reactivities of less active, but readily available, metal powders. Such work is important because these less active powders may be more selective and easier to handle than the activated ones. In a previous report, we have demonstrated that activated nickel and cobalt powders from nickel and cobalt amalgams, respectively, react with aryl halides and benzyl halides to yield the corresponding biaryls and bibenzyls.[4] The activated nickel powders prepared by other methods[1a,b,2] also showed similar activities toward aryl bromides and aryl iodides. To compare the reactivities of these activated metals with less active ones, we investigated the reactions of aromatic halides with commercial nickel and cobalt powders. We report here the results of the exchange reactions between aryl halides and alkali metal halides mediated by these commercial metal powders. The nickel powder selectively catalyzes the aromatic halide exchanges without causing further reaction to give coupling products. The cobalt powder, however, does not exhibit any activity toward aryl halide.

Aryl halides generally do not undergo halide exchange reactions in the absence of a suitable transition metal complex. Finkelstein-type halide exchanges between aryl iodide (or bromide) and cuprous bromide (or chloride) to yield the corresponding aryl bromide (or chloride)[5] were the earliest reported. The reactions are of limited synthetic

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Table I. Results of the Exchange Reactions between Aryl Bromides and Iodide Ion

expt	aryl bromide	time, h	alkali iodide[a]	aryl iodide,[b] %	aryl bromide,[b] %
1	*p*-bromotoluene	24	KI	(86) 73	*c*
2	*p*-bromotoluene	24	NaI	(50)	(51)
3	*m*-bromotoluene	24	KI	(92)	(7)
4	*o*-bromotoluene	29	KI	(80)	(16)
5	*p*-bromoacetophenone	24	KI	73	*c*
6	bromobenzene	21	KI	(83)	(15)
7	*p*-dibromobenzene	15	KI[d]	77	*c*
8	*p*-bromoanisole	24	KI	76	*c*
9	*p*-bromotoluene	23	KI[e]	(>95) 83	
10	*p*-bromoacetophenone[f]	4	KI	75	*c*

[a] All reactions were conducted in DMF at 150 °C. Two equivalents of I^- and a nickel powder 100 mesh in size were used except as otherwise noted. [b] Isolated yields; yields in the parentheses were determined by GC. [c] Not determined. [d] Four equivalents of KI were used. [e] Five equivalents of KI were used. [f] The nickel powder used was <10 μm in diameter.

use due to the fact that aryl iodides, the only aryl halide that cannot be obtained by direct halogenation and yet the most reactive among all aryl halides, cannot be prepared according to the method. Recently, a nickel bromide and zinc powder mixture was found to be an effective catalyst for the exchange of aryl bromide with iodide ion,[6] but the system also produced a substantial amount of biaryl as the byproduct. A number of nickel(II) systems[7] also catalyze the exchange reaction at elevated temperature. However, the nickel(II) species usually are low in catalytic activities and give low yields of exchange products. In the reactions of aryl bromide or chloride with activated nickel powder in the presence of KI, the exchange reaction between aryl halide and KI occurred prior to the coupling reaction and aryl iodide was detected as an intermediate.[1c,4,8]

Results and Discussion

The nickel powder used in the present study is much less active than the one prepared from the amalgam method. One of the most striking differences between these two powders is that the former is stable to air, while the latter starts to burn on exposure to air.[4] The reaction of aryl bromide with the present powder at 150 °C gives no biaryl, in contrast to the results with the activated nickel powders. Attempts to promote the coupling reaction by adding KI to the solution also failed. However, an exchange reaction between the aryl bromide and KI leading to a high yield of the corresponding aryl iodide (eq 1) was observed. The results of the exchange reactions of various

$$\mathrm{RC_6H_4Br + KI \xrightarrow{Ni} RC_6H_4I + KBr}\downarrow \tag{1}$$

aryl bromides as well as the reaction conditions are presented in Table I. In addition to the aryl iodides observed at the end of the exchange reactions, the unreacted aryl bromides and a trace of the corresponding arenes (<1%) were also detected. The coupling products that were obtained as the major species in the reaction of aryl bromides with activated nickel powder were not found under the reaction conditions. The yield of aryl iodide increases as the relative amount of KI increases, as indicated by the results of runs 1 and 9 in Table I.

Although a nickel to aryl bromide ratio of 5/1 was employed in the reaction, the nickel powder can be reused in the same type of reaction more than 10 times without any detectable decreases in activity. Consequently, the powder was acting as a catalyst in the exchange reaction. The purpose of using excess nickel powder is to raise the reaction rate by increasing the nickel surface. If less nickel powder is employed, a longer reaction time is required to achieve the same result.

Pretreatment of the nickel powder has a great effect on its catalytic activity in the halide exchange reaction. In general, a small amount of I_2 was added to the reaction solution, with the aim of creating a fresh nickel surface from the reaction of I_2 with the nickel surface. The effect of I_2 can be clearly seen from the following observation. The reaction of m-$\mathrm{CH_3C_6H_4Br}$ with KI without the addition of I_2 gave 40% m-$\mathrm{CH_3C_6H_4I}$ in 32 h, while the same reaction yielded 92% of the iodo product in 24 h in the presence of I_2 (run 3 of Table I). The enhancement of exchange rate can also be achieved by washing the nickel powder with dilute HCl solution before it is employed as the catalyst.

Because I_2 quickly reacts with nickel to yield nickel(II) iodide during the halide exchange reaction, it is interesting to know whether the nickel(II) species has played an important role in the catalytic reaction. To answer the question, the following experiment was performed. The reaction between p-$\mathrm{CH_3COC_6H_4Br}$ and KI in the presence of 0.05 equiv of I_2 was stopped at 3 h. I_2 was completely consumed, as shown by the disappearance of the deep brown color on cooling of the solution. The metal powder was separated from the solution, which contained the nickel(II) iodide produced from the reaction of I_2 and the metal. The solution was equally divided into two parts. One part was analyzed by GC to give a 61/39 ratio of p-$\mathrm{CH_3COC_6H_4I}$ to p-$\mathrm{CH_3COC_6H_4Br}$. The other part of the solution was further heated at the same temperature for another 3 h. Analysis of the latter solution by GC showed that the ratio of p-$\mathrm{CH_3COC_6H_4I}$ to p-$\mathrm{CH_3COC_6H_4Br}$ was 63/37. The results clearly indicate that the contribution of Ni(II) to the halide exchange reaction is very small compared with that of the nickel powder.

The same nickel powder also catalyzes the reaction of aryl iodide with KBr to produce aryl bromide, suggesting that the exchange reaction is reversible. The reversibility is best demonstrated by the following example. Under the same conditions as described in Table I, the reaction of p-$\mathrm{CH_3C_6H_4Br}$ with 1.5 equiv of KI gave 68% of p-$\mathrm{CH_3C_6H_4I}$ and 32% of p-$\mathrm{CH_3C_6H_4Br}$, while the reverse reaction, that is, p-$\mathrm{CH_3C_6H_4I}$ with 1.0 equiv of KBr and 0.5 equiv of KI, also afforded 69% of p-$\mathrm{CH_3C_6H_4I}$ and 31% of p-$\mathrm{CH_3C_6H_4Br}$. The result indicates that both reactions have reached the state of equilibrium and p-$\mathrm{CH_3C_6H_4I}$ is in equilibrium with p-$\mathrm{CH_3C_6H_4Br}$ at the end of the reaction.

Although the strength of the carbon–iodide bond in aromatic compounds is weaker than that of the carbon–bromide bond, the lack of solubility of KBr relative to KI in DMF drives the exchange reaction of eq 1 to favor aryl iodide. The same technique has been applied in the synthesis of alkyl iodide from alkyl bromide or alkyl chloride.[9]

The effect of solvent on the exchange rate was briefly explored. With the same reaction conditions as shown in Table I, the yield of p-iodotoluene from p-bromotoluene and potassium iodide decreases from 86% in DMF to 69% in HMPA and further down to 14% in ethylene glycol.

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Table II. Results of the Reactions of Aryl Halides with Various Alkali Halides[a]

expt	ArX	MX′/quanity (equiv)	ratio of ArX′/ArX[b,c]
1	*p*-chlorotoluene	KI/1.5	29/71
2	*m*-chlorotoluene	KI/1.5	31/69
3	*o*-chlorotoluene	KI/1.5	26/74
4	*p*-chloroacetophenone	KI/1.5	<5/95
5	chlorobenzene	KI/1.5	<5/95
6	*p*-chlorotoluene	NaI/2	40/69
7	*p*-chloroanisole	NaI/2	44/56
8	*p*-chloroacetophenone	NaI/2	26/74
9	*p*-chloronitrobenzene	NaI/1.5	10/90
10	*p*-chloroanisole	NaI/5	55/45
11	*p*-chloroacetophenone	NaI/8	28/72
12	*p*-iodotoluene	KBr/1 + KI/0.5	31/69
13	*p*-iodotoluene	KCl/1 + KI/0.5	32/68
14	*p*-bromotoluene	KCl/3	46/54
15	*p*-chlorotoluene	NaBr/3	20/80

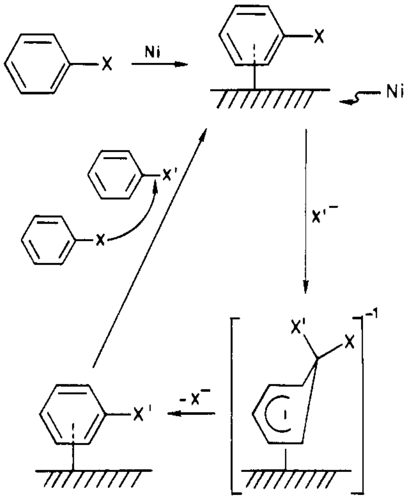
[a] All reactions were carried out in DMF at 50 °C for 24 h with a nickel to aryl halide ratio of 5/1. The particle size of the nickel powder used was 100 mesh. [b] The ratios were determined by GC and ^{1}H NMR spectroscopy. [c] Small amounts of arene (<4%) were also observed by GC in most of these exchange reactions.

The observations parallel the results found in the biaryl synthesis from the reaction of aryl halide and the activated nickel powder prepared from a nickel amalgam.[4]

The exchange of aryl chloride with iodide ion, that of aryl bromide with chloride ion, and the reverse reactions were briefly explored. The results as well as the reaction conditions are presented in Table II. All of these reactions proceed in the presence of the nickel catalyst, but most of them do not reach equilibrium under the reaction conditions as described in Table II. Examination of the results of runs 4–10 of Table II shows that the reaction of aryl chloride with I^- is accelerated by electron-donating groups such as OCH_3 and decelerated by electron-withdrawing substituents, e.g., NO_2 and $COCH_3$, on the aromatic ring. On the other hand, the position of the substituent only slightly affects the exchange rate. For instance, the reaction of KI with the para, meta, and ortho species of $CH_3C_6H_4Cl$ gave, respectively, 29/71, 31/69, and 26/74 ratios of the corresponding $CH_3C_6H_4I$ to $CH_3C_6H_4Cl$. The observation is in contrast to results of aryl coupling reactions by activated nickel powder, which show that the yield of biaryl is much lower with an ortho-substituted aryl halide.[4]

From the foregoing results, it appears that nickel surface is responsible for the catalysis of the halide exchange reactions. In addition, it has been reported that aromatic compounds may be chemisorbed on various nickel surfaces.[10–11] On the basis of these observations, a mechanism for the aryl halide exchange reactions mediated by nickel surface is proposed as shown in Scheme I. The reaction paths involve π-absorption of aryl halide by nickel surface in the first step, followed by the nucleophilic attack of an external halide ion at the aromatic carbon bonded to halide to give an intermediate **1**. Expulsion of the halide and the subsequent desorption complete the exchange reaction. π-Coordination of aromatic ring to metal or metal surface should greatly reduce the electron density on the ring[12] and facilitate nucleophilic displacement reactions. Such enhancement of nucleophilic substitution or addition has been observed in a vast number of π-aromatic transition metal complexes.[13] The decrease in halide exchange rate with electron-withdrawing substituents is surprising in view of the fact that nucleophilic substitution of aromatic compounds is greatly facilitated by electron-withdrawing groups. However, it may be understood in terms of the dramatic decrease of the absorption of these electron-withdrawing species by the nickel surface. This is supported by the fact that π-aromatic transition metal compounds are generally stabilized by electron-donating groups on the ring while destabilized by electron-withdrawing substituents.[14] Alternatively, a mechanism for the halide exchange reactions involving the oxidative addition of aryl halide to the nickel surface, followed by halide exchange and reductive elimination, cannot be totally excluded.

Scheme I



1

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL FX-100FT NMR spectrometer, and mass spectra were obtained on a JEOL JMS-D mass spectrometer. Gas chromatographic analyses were performed on a Shimadzu GC-8A using a 10% Carbowax 20M on a Chromosorb G column. Melting points were determined on a Laboratory Devices Mel-Temp apparatus and were uncorrected.

Nickel powder (100 mesh, Wako; <10 μm, Merck), bromobenzene (Merck), *p*-, *o*-, and *m*-bromotoluene, *p*-anisole, *p*-bromoacetophenone, *p*-chloroanisole, *p*-chloroacetophenone, and *p*-chloronitrobenzene (Tokyo Kasei) were used as purchased.

General Procedures for the Halide Exchange between Aryl Bromide and Potassium Iodide. Example 1. A mixture of nickel powder (2.25 g, 38.3 mmol, 100 mesh), *p*-bromotoluene (1.31 g, 7.62 mmol), KI (2.52 g, 15.2 mmol), I_2 (0.0935 g, 0.384 mmol), and DMF (10 mL) in a flask was degassed and then heated at 150 °C with stirring for 24 h. At the end of the reaction, 50 mL of 3% hydrochloric acid and 20 mL of *n*-pentane were added to the mixture. The nickel powder, which was absorbed on the magnetic stirring bar, was removed, and the organic layer was separated from the aqueous phase. The latter was further extracted twice with the same solvent. The combined organic layers were washed with distilled water twice and dried over magnesium sulfate. Concentration followed by recrystallization from ethanol afforded 1.22 g (73%) of *p*-iodotoluene: mp 33–34 °C (lit.[15] mp 34–35 °C); mass spectrum, *m/e* 218 (M^+). The ^{1}H NMR and IR data of the product agree with the assigned structure.

A number of aryl iodides were obtained by the same procedure, with the exception of *p*-iodoacetophenone, which employed

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chloroform for extraction and acetonitrile for recrystallization. The reaction conditions and the isolated yields are listed in Table I. All of these compounds were characterized by comparing their melting points and NMR and mass spectra with those reported for the same structures. Important data of these products are shown below.

m-Iodotoluene: mp 27–28 °C (lit.[16] mp 28 °C); mass spectrum, *m/e* 218 (M^+).

p-Iodoacetophenone: mp 83–84 °C (lit.[16] mp 85 °C); mass spectrum, *m/e* 246 (M^+).

p-Diiodobenzene: mp 126–127 °C (lit.[15] mp 129 °C); mass spectrum, *m/e* 329 (M^+).

p-Iodoanisole: mp 49–50 °C (lit.[15] mp 51–52 °C); mass spectrum, *m/e* 234 (M^+).

A nickel powder with smaller particle size (<10 μm, Merck) was also employed in the exchange reaction between *p*-bromoacetophenone and KI. The same reaction conditions as those in Example 1 were followed except that the reaction time used was only 4 h. The reaction gave 75% of *p*-iodoacetophenone.

Example 2. A mixture of nickel powder (4.19 g, 71.4 mmol, 100 mesh), KI (4.75 g, 28.5 mmol), I_2 (0.181 g, 0.714 mmol), bromobenzene (1.50 mL, 14.3 mmol), and DMF (10 mL) in a round-bottom flask were first degassed and then heated at 150 °C with stirring for 21 h. To the solution was added 50 mL of a 3% dilute hydrochloric acid and 20 mL of a 1/1 (v/v) chloroform–*n*-pentane mixture. The nickel powder, which was absorbed on the magnetic stirring bar, was removed, and the organic layer was separated from the aqueous phase. The latter was further extracted by the same solvent mixture twice. The combined *n*-pentane–chloroform solution was washed with Na_2SO_3 solution and distilled water and dried over $MgSO_4$. The organic mixture was concentrated and analyzed by GC with chlorobenzene as the internal standard to give 83% of iodobenzene and 15% of unreacted bromobenzene. The relative amounts of iodobenzene and bromobenzene were further determined by ^1H NMR spectroscopy. The results of these two methods are in good agreement.

The reactions of *o*-bromobenzene with KI and aryl chlorides with KI or NaI were analyzed by the same method. The results are shown in Table II.

Acknowledgment. We thank the National Science Council of the Republic of China for support of this work.

Registry No. Ni, 7440-02-0; KI, 7681-11-0; NaI, 7681-82-5; KBr, 7758-02-3; KCl, 7447-40-7; NaBr, 7647-15-6; *p*-BrC_6H_4Me, 106-38-7; *m*-BrC_6H_4Me, 591-17-3; *o*-BrC_6H_4Me, 95-46-5; *p*-$BrC_6H_4C(O)CH_3$, 99-90-1; PhBr, 108-86-1; *p*-$Br_2C_6H_4$, 106-37-6; *p*-BrC_6H_4OMe, 104-92-7; *p*-ClC_6H_4Me, 106-43-4; *m*-ClC_6H_4Me, 108-41-8; *o*-ClC_6H_4Me, 95-49-8; *p*-$ClC_6H_4C(O)CH_3$, 99-91-2; *p*-ClC_6H_4OMe, 623-12-1; *p*-$ClC_6H_4NO_2$, 100-00-5; *p*-IC_6H_4Me, 624-31-7; PhCl, 108-90-7; *m*-IC_6H_4Me, 625-95-6; *o*-IC_6H_4Me, 615-37-2; *p*-$IC_6H_4C(O)Me$, 13329-40-3; PhI, 591-50-4; *p*-$I_2C_6H_4$, 624-38-4; *p*-IC_6H_4OMe, 696-62-8; *p*-$IC_6H_4NO_2$, 636-98-6.

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Charamin, a Quaternary Ammonium Ion Antibiotic from the Green Alga *Chara globularis*

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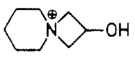
In view of the abundant current chemical investigations of marine algae,[2] freshwater plants have received only little attention from natural products chemists. Among freshwater and brackish water plants characean algae have been noted for their ability to dominate their ecosystems.[3] Earlier reports[4,5] have implicated the insecticidal[6,7] 4-(methylthio)-1,2-dithiolane and the herbicidal[5] 5-(methylthio)-1,2,3-trithiane in an allelopathic defense system in these organisms. Further investigations of *Chara globularis* Thuillier 1799 revealed a pronounced antibiotic activity associated with aqueous extracts of defatted plant material, exposing still another component of the chemical armory of this alga.

Lyophilized *Chara globularis* was defatted and extracted with water to produce, after lyophilization, 6.1% mainly organic material with the ability to significantly reduce the uptake of tritium-labeled glucose by a natural pond population of bacteria. Guided by the latter bioassay a convenient purification procedure consisting of cellulose column chromatography was established. The active fraction was partitioned between chloroform and water, leaving the activity in the aqueous phase. Repeated purification by HPLC gave thymidine, deoxyuridine, and an active compound. At a concentration of 4 μg/mL this material reduced the uptake of tritiated glucose by a natural population of bacteria to about 9% as compared to a control without antibiotic added. Noise- and off-resonance-decoupled ^{13}C NMR in D_2O served to identify the signals as due to methylene groups at 64.5 ppm and methine groups at 74.1 ppm. These values compare favorably with the values of 59.1 and 71.9 ppm observed for the methylene and methine carbons, respectively, of the four membered ring of 4-azoniaspiro[3.5]nonan-2-ol (**1**).[8] In pyridine-d_5 the ^1H NMR (90 MHz) exhibits a multiplet centered around 4.3 ppm comparable to a value of 4.2–4.9 (m, 5 H) or 4.5 ppm reported for the protons of the four-membered ring of **2** in acetonitrile-d_3[9] and dimethyl sulfoxide-d_6,[10] respectively. The multiplet (displaced to 3.6 ppm in D_2O) is resolved at 500 MHz into an ABX system: H_A 3.55 ppm (4 H, dd, J_{AB} 12.0 Hz, J_{AX} 6.2 Hz), H_B 3.64 ppm (4 H, dd, J_{AB} 12.0 Hz, J_{BX} 4.0 Hz), 3.77 ppm (2 H, m). The ^1H NMR spectrum in pyridine-d_5 indicates a water content of 7–8 molecules of H_2O per 10 ABX protons. The water content was substantiated by IR spectroscopy on the solid compound (KBr), where a strong broad absorption at 3000–3500 cm^{-1} (OH_2 stretch) after desiccation of the sample leaves two bands (OH stretch) at 3200 and 3360 cm^{-1} concomitant with decreased intensity of the weak bands at 1600–1630 (OH_2 scissoring) and 400–700 cm^{-1} (coordinated OH_2 rock, twist, and wag modes). The CH_2 deformation mode appears strongly at 1405 cm^{-1}. On the basis of these findings, we propose the structure of the active principle, charamin, to be 4-azoniaspiro[3,3]heptane-2,6-diol (**3**).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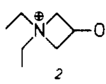
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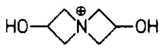
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